THE LEUCOSIS OF FOWLS AND LEUCEMIA PROBLEMS

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11 HANOVER SQUARE, LONDON, W. 1

KØBENHAVN - KRISTIANIA - BERLIN

[1921]

Published at the expense of
The Rask Oersted Fund

PREFACE

I HAVE previously, in German, given an exposition of the pathology of the leucosis of fowls (*Die übertragbare Hühnerleukose,* 1918; Verlag von Julius Springer). In this work, which was already finished in 1914, I gave an exposition of the different types of the disease: the lymphatic, the myeloic and the intravascular lymphoid type, but at that time I was, particularly owing to my imperfect acquaintance with the cytogenesis, cut off from a more thorough comparative-pathologic treatment of the subject. Later examinations have now so much enlightened me as to the formerly dubious types of cells, that I have been able to determine more exactly the nature of "the intravascular lymphoid" leucosis, while I have also got a deeper insight into the cytology of the myeloic leucosis and the varieties of this type. Besides, the exposition in hand has been benefited also in other respects by the experience gained in recent years. On account of the confusion in terminology and concepts, which has characterized the hematology, I have found it necessary to open the exposition with a synopsis of the history of the leucemical diseases and the most important etiological theories. After a brief survey of the blood and blood-forming organs of fowls in normal conditions, I give a description of the chief forms of the leucosis of fowls, after which, in the final chapter, I briefly go through the comparative-pathological questions to which the experiments give rise.

The object of this book is to spread the knowledge of the leucosis of fowls and so cause researches to be taken up to a greater extent than has so far been the case. The study of the leucosis of fowls is for the present the only way open to us for the experimental treatment of the leucemia problems, and there is undoubtedly still a great deal of work to be done in this domain.

V. ELLERMANN.

November 1921.

THE Plates, which are taken from some articles in *Folia Hæmatologica*, are produced by Funke's Lithographical Establishment in Leipzig. The text-figures are produced by Hendriksen's Reproduction Establishment in Copenhagen.

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I

HISTORICAL SURVEY

THE history of leucemia begins with the year 1845. In that year two cases were communicated by Craigie & Bennett in October, and in November one case by Virchow. Descriptions of cases of leucemia had certainly appeared formerly, even as early as the beginning of the 19th century (Bichat, Velpeau), but with the aids then at disposal it was not possible to understand them or to distinguish them from the pyemic affections. It was the introduction of microscopical examination which created new possibilities. Virchow used the designation leucemia for the first time in 1847, and later on he emphasized, and this is certainly right, that this new name had contributed to circumscribe the conception of the disease and to give it currency in medicine. While in the first cases it was the swelling of the spleen that was the predominating feature in the anatomical picture, Virchow made the important observation during continued work in 1847, that cases were found with severe swelling of one and all of the lymphatic glands, while the swelling of the spleen was less considerable. After this one had to distinguish between two forms: the lienal, with the considerable swelling of the spleen, and the lymphatic, with predominant swelling of the lymphatic glands. Also the blood picture was different, as the white corpuscles

were considerably larger in the lienal than in the lymphatic form. Bennett, too, pursued his observations, and in 1851 reported a series of cases which contributed to elucidate the picture of the disease. He proposed the word leucocytæmia as a designation for the disease; this, however, was not generally accepted. Virchow was of the opinion that the red blood-corpuscles developed from the white ones, an opinion which has subsequently proved an error. Considering how new the questions were and how defective the methods, one cannot wonder that he could make a mistake on this point; but he had a clear understanding of the way to go, and with a firm hand laid down the lines of future investigations. Significant in this respect is the following passage in his treatise, *Die Farblosen Blutkörperchen*: "Die Lehre von der Leukämie findet ihren definitiven Abschluss in der Lehre von den farblosen Blutkörperchen. Wo die farblosen Blutkörperchen überhaupt herkommen, da müssen auch die in der Leukämie so massenhaft gebildeten herstammen. . . . Alles kommt darauf an die Bildungsstätten festzustellen."

The solution of these questions devolved upon other investigators. In 1867 Cohnheim discovered that by inflammation the white corpuscles emigrated from the blood to the tissues. By this discovery the resemblance between leucocytes and pus-cells which Virchow had maintained so firmly, received its natural explanation, while the question whether the leucemia-cells were white blood-corpuscles or pus-cells, lost every importance.

Of far wider consequence to the leucemia doctrine were the researches of Neumann. Neumann proved in 1868 that in the bone-marrow there were nucleated red corpuscles, which in all respects agreed with the red blood-corpuscles in the life of the fœtus.

This proof is one of the main pillars in our knowledge of blood-formation. Every theory of red corpuscles being a further development of the white ones, had after this to be rejected. In his examinations of the bone-marrow, Neumann further perceived the resemblance between the

colourless marrow-cells and the white blood-corpuscles, from which he concluded that the bone-marrow was probably the place where the white corpuscles were formed. In leucemia the bone-marrow had not hitherto been examined, and here in one case Neumann succeeded in pointing out a pronounced change, the marrow being in colour and consistence like tough, mucous pus, as well in the long bones as in the mask-spaces of the spongeous bones. From these findings Neumann drew the conclusion that in leucemia the disease of the bone-marrow would have to be regarded as a very essential factor in the origin of the leucemical blood-change, and that besides the lienal and the lymphatic form, a myelogen form would have to be set up.

However essential the progress following from Neumann's discoveries, the question of the origin of the leucocytes was by no means elucidated with certainty. Ehrlich's investigations were the first to clear up this point beyond doubt. By using new ingenious methods such as dry preparations, fixing in heat, and staining with acid, basic or neutral dyes, Ehrlich succeeded in pointing out morphological and chemical peculiarities, especially differently reacting protoplasm-grains, thus characterizing with a hitherto unknown accuracy the different leucocyte forms as well as their mother-cells. The leucocytes of the blood compared with the marrow-cells, showed, moreover, that regular changes in the shape of the nucleus took place, so that from this it was possible to find out the age of the cell. On this basis Ehrlich could distinguish two main strains of leucocytes, viz.: (1) Polynuclear, granulated, which are formed in the bone-marrow; and (2) lymphocytes which are derived from the lymphatic glands and the lymphatic tissue in other places. In accordance with this he could refer the leucemias to two kinds, the myelogen and the lymphatic.

In the myeloic leucemia there is a hyperplasia of marrow-tissue, not only in the bone-marrow, but also in the other organs, viz., the spleen, liver and lymphatic

glands, and the blood is overflowed with granulated marrow-cells, partly fully developed polynuclear leucocytes, partly their mother-cells, the granulated marrow-cells (myelocytes). In the lymphatic leucemia there is a hyperplasia of the lymphatic glands and the remaining lymphatic tissue (spleen follicles, gut follicles and the small accumulations of lymphocytes in liver and kidney), while the lymphocytes or their pre-phases are to be found in great number in the blood. As the lymphatic tissue normally is found dispersed in various places in the organism, Ehrlich regarded the lymphatic leucemia as an affection of the whole system of lymphatic organs; on the contrary, he regarded the myeloic leucemia as a disease of the bone-marrow, being of the opinion that the development of myeloic tissue in other organs was due to a metastasis from the bone-marrow. The reason of this was that under normal conditions myeloic tissue was not, like the lymphatic tissue, to be found here. Embryological investigations, however, subsequently showed the interesting fact that the organs, which in myeloic leucemia undergo a marrow-like transformation (liver, spleen, lymphatical glands), are myeloic organs in the fœtal life. This has been the chief reason why M. B. Schmidt, and with him the majority of investigators, regard the heterotopic marrow-tissue as autochthonic formations (formed on the spot) and not as metastases.

The main stress was after this removed from the macroscopical post-mortem findings which had proved useless as a principle for classification to the microscopical demonstration of the nature of the hyperplastic cells. A firm foundation for all later examinations had been laid.

Ehrlich's clear scheme, which thus assumes a consequent bipartition of the leucocytes and their mother-cells, as well in healthy as in morbid conditions, has been contested especially on the part of normal anatomists, and scientists have formed two camps: the dualists, who agree with Ehrlich's doctrine, and the unitarians, who consider the various leucocyte forms as developments of

one and the same strain. The unitarians who partly relied on embryological examinations, had for some time the lead; but of late there has appeared a series of facts, which have given great support to the dualistic doctrine.

Primarily, mention must here be made of the investigations on leucemia and anemia undertaken by Meyer & Heineke in 1907. The chief result of the exact histological examinations made by these researchers was the demonstration of the fact that the histogenesis differed essentially in the two forms of leucemia, as proliferation in the lymphatic leucemia originated in the lymph-follicles of the spleen and lymphatic glands, while these were passive or expelled in the myeloic leucemia. In the latter the proliferation, as regards the spleen and the lymphatic glands, proved to originate in the extra-follicular tissue. Of great importance was next the demonstration of the existence of "lymphoid" cells, which in a purely morphological respect resemble lymphocytes, in so far as they have a large nucleus and a non-granular protoplasm, but in effect have nothing to do with lymphocytes. These cells, the interpretation of which has been attended with great difficulties, were, of course, able to give rise to false unitarian conclusions. The most important of these cells are the myeloblasts and the lymphoid erythroblasts.

The myeloblast doctrine began with Hirschfeld's work in 1898. Hirschfeld found in embryonal bone-marrow non-granular cells which showed all stages of transition to typical granular myelocytes in the form of partially granulated cells. The term "myeloblasts" itself is derived from Nægeli, who in 1900 pointed out such cells in the bone-marrow in different diseases, especially in pernicious anemia and typhus, and who regarded them as pre-phases of myelocytes, whence the name. Nægeli's theory was supported by investigations made by Schridde and by Horwitz. Also from other sides (Schwarz, Helly) it is maintained that myeloblasts by no means is a constant and necessary pre-phase to the myelocytes, and though

later examinations (Helly, Ellermann) have proved that the so-called myeloblasts in pernicious anemia in reality are pre-phases to red blood-corpuscles (erythrogonies), the myeloblast doctrine nevertheless denoted an advance. It was now clearly understood that some cases of acute leucemia which were formerly taken for lymphatic, in reality were myeloblast leucemias. Hence it is at times difficult or impossible to distinguish morphologically between myeloic and lymphatic leucemia, at any rate by means of the blood-picture ; but that by no means implies that the cells in question are identical ; on the contrary, in the present state of knowledge the dualistic viewpoint must be maintained, and the fact itself, that non-granular myeloic cells are to be found, is also admitted by the antagonists of the myeloblast theory.

Our knowledge of the lymphoid erythroblasts dates from 1883, when Löwit found erythroblasts containing more or less hemoglobin, as well as quite hemoglobin-free erythroblasts in salamanders. He pointed out similar conditions in the liver of the embryos of mammals, and even in the post-embryonal organism in mammals there were, though more seldom, hemoglobin-free erythroblasts in the blood-forming organs. In accordance with this Denys proved in 1887 that in the bone-marrow of birds normally there was to be found hemoglobin-free cells that were pre-phases to red blood-cells. Bizzozero, who in 1890 dealt with the same subject, certainly objected to Denys' results that his method was not able to demonstrate very small amounts of hemoglobin ; but regarding this point the real difference between these two works is, that cells, which Denys regarded as hemoglobin-free erythroblasts, are taken for leucocytes by Bizzozero. Only much later (1908) do we meet with a description and a picture of such cells in human blood in a work by Pappenheim, whose observations are confirmed by Ferrata & Negreiros-Rinaldi (1914).

That which characterizes these lymphoid erythroblasts is partly the regular, round, strongly coloured nucleus, partly the very much pronounced basophilia of the proto-

plasm. Thus the peculiar phenomenon (Ferrata's "fenomeno paradosso") is here met with, that the origin cells of the acidophile erythrocytes are more basophile than, for instance, the leucocytes. It may surely be taken for granted that the lymphoid erythroblasts have generally been misinterpreted and regarded as leucocytes, which they certainly resemble very much. Even more difficult than in dry-preparations is the identification when dealing with sections of organs. This matter is touched upon in the above report of the myeloblasts.

According to Virchow's definition, leucemia was a disease, the essential features of which were an augmentation of the leucocytes in the blood and a hyperplasia of the organs connected with the blood-formation. Of these phenomena the blood-change is the most striking and peculiar, for which reason it appeared natural that the disease got its name after this. Even Virchow reports, however, that there are to be found cases as well of lienal as of lymphatic leucemia, in which the blood change does not appear until the disease has lasted for months or years. Cases are, however, met with, in which a leucemic state of the blood does not occur at all. The first case of this kind was reported in 1865 by Cohnheim. The patient was a man aged 24, in whom the clinical examination disclosed a considerable swelling of the spleen, but no augmentation of the leucocytes in the blood, and by autopsy there was found a swelling of spleen and severe swelling of the retroperitoneal glands. The microscopical examinations revealed numerous very large follicles in the spleen, periportal accumulation of myelocytes throughout the liver and severe interstitial infiltration of lymphocytes in the cortical substance of the kidneys. Cohnheim was not able to classify this case. The resemblance to leucemia was evident, but why did the change in the blood which might be expected in consequence of the severe hyperplasia fail to appear? Cohnheim's conception of the change in the blood as pathognomic to the disease explains his term "Pseudoleucemia," *i.e.* a disease which resembles leucemia, but in reality

differs from it. Later examinations (Pincus, Pappenheim and others) now proved that this term was misleading, in so far as the pseudo-leucemias (apart from the cases of granulomatosis, tuberculosis, etc.) were just as genuine cases of the disease as the leucemias proper, and that the change in the blood was a symptom to the presence or absence of which one could not attach fundamental importance. This view, to which great support has been given by the recent examinations undertaken with a better technique, meant a revision of the whole conception of the disease, and compelled new designations. The term pseudo-leucemia was awkward for several reasons. Partly it was misleading to keep on calling some cases false, though they were known to come within the scope of the disease, partly the term gradually came to be used also for other conditions which only had a purely superficial resemblance to leucemia, but which in reality were essentially different from it. To resort to the term leucemia also in cases in which the change in the blood is lacking has too much the character of self-contradiction. Furthermore, the term is still suitable to denote the symptom : the leucemical blood change, for which it may be used without any essential change of meaning worth mentioning. This sense is also implied in the adjectives leucemic and aleucemic, as they are now generally used. The terminology has developed in three different directions : (1) It has been attempted to replace " pseudo-leucemia " by a better designation, viz. aleucemia (Orth). This term has undeniably the advantage of not including different conditions for the present, but is not good logically regarded, as the lack of leucemia is a purely negative sign which could be used as well for quite different conditions. (2) More rational was the terminology which took into consideration the constant chief feature of the disease and radically refused to use an inconstant symptom like leucemia as a base for classification. Türk's designation, lymphomatosis, and Hirschfeld's, myelomatosis, were the first proposals in this direction, which do not, however, seem to have gained currency ; while, on the

contrary, Schridde's shorter and correcter words, myelosis and lymphadenosis, are now used in several text-books and so have more chance of being generally accepted. (3) Finally, it must be mentioned that Ellermann & Bang have proposed the word " leucosis " as a common designation for leucemic and aleucemic cases, myeloses as well as lymphadenoses. In my opinion this word has several advantages. Partly it is to indicate the common factor : the abnormal production of leucocytes, without making the conditions of the blood the decisive circumstance ; partly the word has quite practically the advantage of being very much like the old familiar word leucemia. It has proved very practical in the study of the leucemical disease of fowls, but is now also used by several writers as a collective name for corresponding affections in man.

II

ETIOLOGICAL THEORIES

WHILE our knowledge of the anatomical and clinical circumstances of the disease has constantly progressed since 1845 and now provisionally seems to have reached a final stage, we are to-day nearly as ignorant as in the time of Virchow as to the cause of the disease, and the only luminous point is, as we shall subsequently see, the results of the experiments of the leucosis of fowls. Mentioning the causalities, therefore, means mentioning the theories. These, of course, bear the impress of the knowledge of the different times. At first, for instance, the idea of a traumatical etiology seemed not unlikely. As late as 1897, Carl Lange says "that the usual inclination to interpret the illness as infectious does not fit in with the only fairly certain fact in the etiology of leucemia, the fact, viz., that it can develop as the consequence of a trauma." The progress of bacteriology suggested the question whether leucemia too might not be caused by an infection. Similarly the revival of the doctrine of tumours and later on the doctrine of hormons gave rise to leucemia theories.

While quite briefly enumerating these theories, I must emphasize that they are of very different reach, and that the acceptation of one theory does not necessarily exclude another. On the contrary, it is possible that every one of the theories contains a grain of truth, and so perhaps will contribute to the final theory; the traumatic theory, which, at any rate, can only be used in a minority of cases, cannot be a real etiological theory; but at best we may suppose that the trauma can form a disposition

in the same manner as in traumatic pneumonia and other traumatic internal diseases. When the tumour theory is discussed in contradistinction to the theory of infection, this by no means implies that a decided stand is taken in the question of the tumour etiology, and that the infective origin is here excluded, but only that for various reasons, tumours are temporarily kept distinct. Nor is the tumour theory, in spite of its wider view, a proper etiological theory. The same is true of the theory of correlation, which may be more or less well founded, but says nothing about the actual cause which is the condition of the want of harmony in the joint action of the organs. This theory might thus in so far be reconcilable to the theory of infection, which is the only one which may by rights be named an etiological theory.

The Traumatic Theory

In the literature there are communications about traumatic leucemias as early as 1876, but cases are getting more frequent of late years owing to the legislation providing for the insurance of workers against accidents. Besides, none of the published cases are particularly convincing. Stern rightly points out how loosely founded the argumentation in reality is. Thus it is often stated that leucemia may arise after larger bleedings or hematoms, produced by small wounds or contusions ; but probably cause is here confounded with effect, so that the leucemia is present before the trauma and disposes to bleedings, even with small traumas. The same is the case with the frequently mentioned trauma in the region of the spleen. Owing to the trauma, pains will arise in the diseased spleen, and only then will the patient notice the disease, which will then be considered a consequence of the trauma. The whole basis is therefore exceedingly unstable and cannot be otherwise, because one cannot reckon upon being able to demonstrate a direct connection in time between trauma and disease. Possibly experiments on

animals will some day bring clearness in this problem, but if the trauma should really prove to be of importance, at any rate it will only come into question as a realizing factor and not as the specific cause.

The Tumour Theory

Owing to the strong, at times simply tumour-like growth of the leucemic infiltrates, and owing to their growing into the neighbouring organs and their spreading in the organism, which to a certain extent called to mind tumour metastases, various investigators (Bard, Banti, Ribbert) have attempted to place leucemia under the malignant tumours. A closer consideration will, however, show that there is an essential difference between leucemia and the malignant tumours. A carcinoma or a sarcoma begins in one single limited place in an organ, and later on forms daughter tumours in the different organs by the tumour-cells growing into the vessels, and being carried with the blood- or lymph-stream to other places. These secondary " metastatical " tumours appear in greatly varying number and are irregularly dispersed. In leucemia, on the contrary, a whole system of organs is attacked at once. When every follicle in the spleen is in proliferation, and when round every little branch of the portal vein in the liver a lymphatic infiltration is to be found, it cannot be explained by metastatical seed, it must be the effect of an agency which is independent of cellular elements. Against the tumour theory may be urged that the newly-formed cells may in leucemia very well go into the neighbouring organs, whose components are pressed together or pushed aside ; but they are not in possession of the resolving power (of fermentative nature ?) which the proper tumour cells possess, and by which they entirely destroy the organs attacked. How much stress one will lay on this difference is perhaps a matter of judgment ; but at any rate the above-mentioned " systematical " diffusion of the leucosis speaks

absolutely against co-ordinating it with the metastating tumours. On the other hand, it must be emphasized that there are cases of leucosis in which the hyperplasia in a limited part shows a particular energy of growth, so that a kind of tumours are formed (*e.g.* the myeloic chloromes, the lymphosarcomas in the thymus, etc.). These cases to a certain extent form a bridge from the typical leucosis to the tumours ; but for the present they do not help us to an etiological explanation.

The tumour theory is stated in a somewhat different form by Sternberg. Sternberg wants to separate the large-celled cases from the lymphatic leucemias as a distinct group, leucosarcomatosis, because he is of opinion that actual tumour formation, essentially different from the typical leucemia, is here involved. Most pathologists, however, do not accept Sternberg's opinion, partly referring to the above-mentioned arguments against the tumour theory, partly emphasizing the impossibility of separating the leucosarcomatosis as a disease differing from leucemia.

The Correlation Theory

Ziegler thought he was able to show (1906) that by X-raying various experimental animals it would be possible to produce an experimental leucemia. As in these experiments an atrophy of lymphatic tissue was found, and a hyperplasia of myeloid tissue, Ziegler imagined that the real leucemia was produced by the normal balance between the lymphatic and the myeloic tissue being upset in one way or other, *e.g.*, as a consequence of an infectious disease. Thus a primary lesion of one tissue-system would occur and after that a secondary hyperplasia of the other. To such an explanation of the experiments and their application to the spontaneous leucemia it has been objected that the atrophy of the lymphatic apparatus need not be caused by the myeloic hyperplasia, but that perhaps the reverse is the case ; further, that in the experimental animals a leucemoid state might be produced, but not a proper

leucemia ; and, finally, an argument which is rather decisive, that a slighter hyperplasia of lymphatic tissue may now and then be found in the myeloic leucemia, whereas, conversely, in lymphatic leucemia undamaged myeloic tissue may be found in the bone-marrow. Thus a primary atrophy of the one tissue-system is not to be found, and when an atrophy occurs it must be regarded as quite secondary. Ziegler's theory, which is built up on a wrong explanation of the experiments and of the histological circumstances in spontaneous leucemia, is for these reasons a failure ; but even if its foundation had not been wrong, one would miss an explanation of the primary lesion, the reference to a preceding infectious disease presenting a vague supposition instead of a proof.

The correlation theory was adopted by Nægeli in a somewhat altered form (1913). Instead of the unproved antagonism between the myeloic and lymphatic tissue-system, Nægeli assumes an influence of all endocrineous organs on the blood-forming tissues. In support of this he quotes, partly that in normal circumstances a peculiar alternation of myeloic and lymphatic tissue is found in the different periods of life, which can only be conceived to be regulated by a hormonal action, partly that in diseases of the endocrineous glands (*e.g.* myxœdema, Addison's disease) there is an influence on the blood-forming organs, which appears as anemia. Now, of course, there is no more doubt that the finely adjusted balance in the action of the organs also involves the blood-forming tissues, and that there exists a chemical regulation of such processes as production and demolition of the red corpuscles, formation of white blood-corpuscles, etc., but from here there is indeed a far cry to looking upon the leucemical hyperplasias as the result of a defective or morbidly increased hormonal action, particularly as there is no evidence at hand of pathological processes in the endocrineous glands. In order to prove such, it would be requisite to demonstrate palpable anatomical alterations as well as the peculiar clinical phenomena which necessarily accompany them.

This has not, however, been done, so that the theory of correlation also in Nægeli's form has no real basis. That derangements of correlation will be found in leucemia is not unlikely, but probably these, like the atrophy, are quite secondary processes. Whether they will be of any importance in a pathogenetic theory is thus questionable. A causal theory cannot, at any rate, be based on these purely hypothetic derangements of correlation

The Infection Theory

This is to a smaller extent definitely associated with certain names, but it has constantly been in the air, and has been admitted or rejected by investigators, often more on the basis of a general impression than because there were stated arguments to lean upon. Earlier investigators seem to have been inclined to regard leucemia as the result of a *specific infection*. This opinion is clearly stated by Virchow in the following passage : " Will man die Elemente betrachten als Träger der Dyskrasie und als Bedingungen der Metastase, so liegt es wenigstens nahe anzunehmen, dass durch sie ein contagiöser Stoff transportiert wird und eine Inoculation an einem anderen Orte erfolgt, welche diesen Ort zu einer analogen Entwickelung bestimmt, wie die Primärstelle sie erfahren hatte."[1] By the commencement of the new century, Leube maintains in the work, *Die deutsche Klinik*, etc., that in spite of the disappointments in regard to Löwit's parasites, we must maintain the assumption of a specific agent which has influence on the formation of the white corpuscles. It seems, in recent years, as if one is more inclined to accept a *non-specific infection* and suppose a causal connection of that kind that " infectional toxical processes of different kind prepare the soil for the leucemic disease, in which a particular disposition of the tissue, *e.g.* lymphatic constitution or the like, must also be reckoned with as a contributing factor " (Domarus in Kraus's & Brugsch's *Manual*, 1913).

[1] Die Krankhaften Geschwülste, ii.

More important, however, than such opinions are the facts which with more or less justice are brought forward in support of the theory of infection. These can in the main be referred to three groups—clinical observations, demonstration of microbes and transmission experiments.

Clinical observations.—Here we must first mention some cases which look very much like communication by contagion. The first of these cases is communicated by Obrastzow in 1890. A 30-years-old male nurse, who was attending to a patient suffering from acute leucemia, was taken ill 41 days after the death of the patient, and had quite the same symptoms: hemorrhagic diatesis, fever, necrotic angina, increase of the white corpuscles. While the disease in the first patient was of 29 days' duration, the course was still quicker in the attendant, who died after having been ill for 15 days only. The other case, which is communicated by Cabot, was also apparently contagion of a male nurse. He was taken ill shortly after he had nursed a patient suffering from myeloic leucemia for a long time, and died after having been ill for a few months. A third case is communicated by Bie in 1910. A servant living in the house of a patient suffering from myeloic leucemia, and whose work for one thing was to do the bedroom, was taken ill in June 1909, a few months before the death of her master, and in February 1910, when she was admitted to "Rigshospitalet," was very much fallen off. The examination showed a typical case of myeloic leucemia. As far as I know, only these 3 cases have occurred, and the possibility must, of course, be taken into account that it might be quite accidental coincidences. Bie, however, emphasizes that, as leucemia is a rather unusual disease, a coincidence like this would hardly occur, since, according to the calculation of probabilities, there would be 2000 years between every time it would happen! Leucemia seems at times to be endemic. At any rate there is one observation which may be explained in this way. In the course of a couple of years 3 cases of myeloic leucemia were admitted to the surgical

clinic in Heidelberg, all of them coming from a small limited territory, viz., the lower Enzthal, between Phorzheim and Mühlacker. Consequently Arnsperger himself examined the circumstances on the spot, and found 2 patients suffering from myeloid leucemia, whom he examined. Further, the local doctors gave the information that, in the preceding years, 6 patients had died, of whom, at any rate, 4 may be supposed to have been suffering from leucemia, while the diagnosis for 2 of them was more dubious. Altogether it was a striking accumulation of cases, and Arnsperger also quotes it in support of the parasite theory. Finally must be mentioned the family occurrence which is sometimes met with. Casati speaks about a family in which a girl of 10, her father and father's mother, were suffering from leucemia. Eichorst found leucemia in father and son, Biermer in 2 sisters aged $4\frac{1}{2}$ and 3, Senator in twins aged $1\frac{1}{2}$. I cannot answer for the correctness of the diagnosis in these cases, partly because the originals of the works have not been accessible to me. The possibility of a confusion with family hemolytic anemia and anemia pseudo-leucemica infantum must particularly be kept in mind.

There are also cases at hand in which the diagnosis cannot be doubted. Arnsperger informs us that the sister of one of the patients examined by himself had died from leucemia 10 years before. Weiss first mentions an earlier American case, in which 3 sisters, one after the other, were attacked by acute leucemia; and next he records the following personal observation of leucemia in 3 brothers and sisters. The first brother suffered from lymphatic leucemia for 5 years. Some years later the sister was attacked, and died $4\frac{1}{2}$ years later. Finally, the second brother was taken ill, also with lymphatic leucemia. This case had a very acute course, and the patient died a month after the recognition of the illness. Barrenschen reports a case of acute leucemia in a woman aged 38. Death ensued after only 7 days of illness. Shortly after her brother was admitted to hospital suffering from a

typical lymphatic leucemia, and on closer questioning the information was obtained that a cousin about 1 year before had died from an illness which, according to the given information, was undoubtedly a leucemia.

Is it a question of a constitutional family disease in these cases, or is it contagion from one member of the family to another ? To me it does not seem unlikely that there may be a certain family disposition to the disease. The circumstance, however, that several members of the family are attacked shortly after each other, cannot be explained only by family disposition, but speaks most in favour of the theory of infection, so that these cases may be placed on a level with those which are recorded by Obrastzow, Cabot and Bie.

Antagonists of the infection theory will here be able to urge that one might expect to meet with such cases much more frequently if leucemia really were a contagious disease. To this it may be remarked that the contagiousness of several diseases was for a long time not understood (*e.g.* tuberculosis, meningitis, etc.). Various causes may be concurrent to this : (1) A long time of incubation will make it difficult to point out the connection between the single cases. (2) Differences in the clinical picture (leucemic, anemic cases) will work in the same direction. (3) The existence of healthy intermediate links. If such microbe carriers exist, and especially if they are more frequent than those which are attacked by the disease, it will further impede the demonstration of the contagiousness of the disease.

Demonstration of microbes.—It made no little sensation when Löwit, who was known as a trained investigator, stated that he had found a protozoon which he supposed to be the cause of leucemia. It appeared, however, on repeated experiments by other investigators (Türk, Hirschfeld) that Löwit had been wrong, and that the hemamœbes in reality were only parts of cells and other artefacts. Nor can any etiological importance be attached to the parasites or parasite-like formations met with by

Pawlowsky, Proescher and Pappenheim. On the other hand, in many cases of leucemia, particularly in the acute forms, microbes have been found which in themselves are sufficiently certain, but whose importance is very variously appreciated. Thus streptococci and staphylococci, coli-, paratyphoid-, diphtheria-, pseudo-diphtheria-, influenza-, capsule-bacilli, pyocyaneus and others have been met with. While some investigators declare them to be devoid of etiologic importance and regard them only as an accidental secondary find, others place them in more or less direct connection with the disease. This is particularly the case with acute leucemia, which Sternberg even interprets as a variety of the usual septic infection. Such a complete distinction between the chronic and the acute leucemia is, however, quite arbitrary and at variance with facts, for which reason most hematologists do not accept it. On the whole it is natural, owing to the inconstancy and heterogeneousness of the findings of bacteria, to suppose that we have here to do with the secondary infection so well known from the pathology of infection.

Transmission experiments.—In preference to the other theories, the theory of infection has the advantage of being to some extent a working theory which has given rise to investigations. In the literature there is a considerable series of communications about the attempts to produce leucemia in animals by grafting with blood or organs from leucemic human beings or animals. According to their plan these experiments may be classified homologous or heterologous, according as the inoculation is made on healthy animals of the same kind or of a different kind. As in most cases human material is employed, the heterologous inoculations are the most frequent. Only a single investigator (Schupfer) has made a homologous experiment with human material, when he grafted 4 patients suffering from cancer with leucemic blood. Neither of them got leucemia; but the value of this experiment is not great, however, as one could not beforehand take it for granted that cancer patients present the

same susceptibility as healthy persons. At any rate, one of the patients, who died only a month after the inoculation, must be rejected, so that the experiment at best comprises only 3 individuals, a number which is too small to permit of any conclusion from experiments with a negative result. In the present table is given an account of the heterologous experiments which I know, but one can surely take for granted that a great deal of experiments owing to their negative result have never been published.

TABLE I

Heterologous Inoculations

Writer.	Year.	Material from	Grafted on
Mosler . . .	1872	Human beings.	Dogs, rabbits.
Nette . . .	1890	,,	Monkeys, pigs, rabbits, mice, fowls.
Teichmüller . .	1899	,,	Guinea-pigs, mice.
Angebaud . .	1908	,,	Guinea-pigs.
Ottenberg . .	1909	,,	Monkeys.
Hirschfeld & Jacoby	1909	,,	Monkeys, fowls.
Hirschfeld & Wechselmann . .	1909	,,	Fowls.
Lüdke . . .	1910	,,	Monkeys.
Ellermann . .	1912	,,	Rabbits.
Müller . . .	1913	,,	Monkeys.
Wiczowsky . .	1913	,,	Fowls.
Schmeisser . .	1915	,,	Monkeys.
Leschly & Thomsen	1917	,,	Monkeys.
Ellermann . .	1920	,,	Fowls.
Ellermann & O. Bang	1909	Fowls.	Rabbits, guinea-pigs, doves, guinea-fowls, turkey.
Hirschfeld & Jacoby	1909	,,	Rabbits, guinea-pigs, doves.

All of these experiments, except that of Wiczowsky, were negative. A hen grafted with an exudate of pleura from a patient suffering from leucemia got a leucemia 6 weeks later, with a blood-picture which was similar to that of the patient, but different from the usual in the leucemia of fowls. The description of the post-mortem findings and the microscopy seem to indicate that there really was present a leucemic disease ; in view of the negative

results of experiments made by Hirschfeld, Jacoby, Wechselmann and Ellermann, however, the possibility must for the present be reckoned with that it may have been a spontaneous case, which at the beginning of the experiment was in the stage of incubation. As the total number of animals grafted in the experiments is considerable, and as several investigators (Teichmüller, Ellermann, Leschly & Thomsen) have used a larger number of experimental animals, one is justified in drawing the conclusion that heterologous graftings are not able to produce the leucemia, not even when the grafting is made on animals in whom spontaneous leucemia is met with.

If next we regard the homologous experiments, at any rate in the case of a single kind of animal, viz. fowls, positive results have been attained. The first experiments of this kind were instituted in May 1907 by Ellermann & Oluf Bang, and the result was published in *Centralblatt für Bakteriologie*, 1908. Their experiments were confirmed by experiments made by Hirschfeld & Jacoby and by Schmeisser. Besides, leucemia is met with in various animals, viz. dog, cat, bull, horse, pig, mice and hens. The result of the experiments, which only include 4 of the above-mentioned kinds of animals, is set down in Table II.

TABLE II

Homologous Inoculations

Writer.	Year.	Kind of Animal.	Result.
Bollinger . . .	1874	Dog.	o
Weil & Clerk . . .	1904	,,	o
Lüdke	1910	,,	?
Haaland	1911	Mice.	o
Knuth & Volkmann . .	1916	Bull.	o
Ellermann & O. Bang .	1908	Fowls.	+
Hirschfeld & Jacoby .	1909	,,	+
Ellermann . . .	1914	,,	+
Schmeisser . . .	1915	,,	+
Magnusson . . .	1915	,,	+
Ellermann . . .	1920	,,	+

It will be noticed that all the investigators have succeeded in transferring the leucosis of the fowls, but as regards the other animals only a single questionable result has been arrived at, viz., Lüdke's transmission of leucemia from one dog to another. Out of 6 dogs which were grafted intravenously with organs from myeloic leucemia of a dog, 1 got a leucemic alteration of the blood (85,000 leucocytes out of which 5–10 per cent. myelocytes) 4 weeks after the inoculation. This state vanished entirely after the course of 3 weeks. Autopsy of the animal is not mentioned. In the other homologous transmission experiments the number of the animals used is rather small, apart from the experiments with mice (Haaland) in which a great number of animals was used.

Thus the leucosis of fowls is the only leucemic disease in which transmission to healthy animals has proved successful beyond doubt; but as the experiments on other animals have not been carried through to the same extent, and most frequently only comprise very few animals, there are for the present grounds for supposing that homologous experiments on other kinds of animals, correctly carried out, will be able to give a result.

It must be remembered that the leucosis of fowls will certainly admit of transmission, but the inoculation may nevertheless fail, owing to various reasons. Thus it has happened to me that, after 3 successive inoculations with different material, and each time by grafting, on 8 animals, I got a negative result. Not until the fourth inoculation did I succeed after having used 32 animals.

In so far as the leucosis of fowls may by rights be coordinated with the leucemic diseases of man, which I shall try to show in the following, consequently the infectious nature of the leucosis of fowls affords an argument which may with some justice be brought into the field when the point is to show the probability of the infection theory for the human leucemia. Of course it would be still better if one could succeed in transmitting the disease in other kinds of animals, especially the mammals.

III

TECHNICAL REMARKS

The Experimental Animals

BEST fitted for the experiments are chickens or young fowls. Animals which are not lively and which have not a very red comb should not be used. Before the experiment a hemoglobin test should be made and dry preparations examined. Tuberculous animals must be removed as soon as possible, on account of the danger of infection, and because they are unsuitable for experiments. Fowls suffering from tuberculosis have often a whitish, dry comb. On examination of the blood an alteration of the rod-bearing, polynuclear leucocytes is found. The fowls are fed with oats, maize and bread. To avoid diseases of nutrition they must have fresh vegetables: beets, cabbage, potatoes, etc. Furthermore, out of regard to the mechanical treatment of the food in the stomach, they must have gravel with the food. During the experiments it is most practical to keep the animals in small cages. A cage of the size $57 \times 67 \times 107$ cms. will be sufficient for 8 fowls.

Technique of Inoculation

As leucosis is transmitted most surely by intravenous inoculation, this little operation, which is by no means always easy, must be mentioned in a few words.

The arm vein is sought out at the point at which it crosses the under-arm just below the elbow-joint. In this

spot there is a firm support, which is absolutely necessary. If, on the contrary, it is attempted to undertake the injection into the vein in its course over the upper part of the arm where the support is lacking, the inoculation will not succeed. The inoculation is not difficult in young fowls, but the tough skin of the older ones may cause considerable trouble. In such cases the best thing to do is to denude the vein by a little cut. If the inoculation is successful the fluid will run in by a slight pressure on the piston. If, on the contrary, the injection is made into the connective tissue instead of the vein, a certain resistance is felt, and it will be noticed that an œdema will form. In that case the operation must at once be discontinued and the vein in the other wing tried.

Autopsy

The abdomen is opened by a curved cut below sternum. In doing this one has to be very careful not to injure the intestine. Both sides of the ribs are next cut through, and the sternum is bent up towards the head. The stomach is loosened by dull preparation, and behind this the little spleen is found. The kidneys, which have several deep indentations corresponding to the irregular back wall, are carefully prepared out. Then the stomach-intestinal tube and liver are removed. The taking out of the organs does not cause any trouble, however. Bone-marrow is procured by splitting the tibia and femur lengthwise by aid of a pair of strong scissors. In the case of leucosis the following organs must primarily be examined: liver, spleen, kidneys, bone-marrow, thymus, skin, bones, intestine. The size of the organs must be determined by weighing. The weight of the liver is normally 30 to 40 grs., of the spleen 1·5 to 2·5 grs., and of the right kidney about 6 grs.

Histological Examination

For the fixation is used either formalin or, which is

preferable, some pieces are fixed in formalin and others in sublimate.

For formalin fixation is used a solution of one part concentrated formalin to 9 parts distilled water. The solution must be freshly made, and the concentrated formalin must be kept neutral by putting small pieces of marble in the bottom of the bottle.

The fixation takes 2 or 3 days. The sublimate fixation is carried out with the ordinary sodium chloride-sublimate solution. As a rule, I have preferred the following solution: concentrated formalin 1 part, sodium chloride-sublimate solution 19 parts. In this way a very successful fixation is obtained. After 24 hours' fixation the pieces are transferred into 70 per cent. alcohol, to which is added a little iodine spirit. In this the pieces are kept as long as the alcohol is decoloring, and are afterwards treated in the usual way. They are melted down in paraffin and cut in sections, not thicker than 5 μ. For staining is used Hansen's hæmatoxylin for 5 minutes. The sections are kept in distilled water for 10 to 15 minutes and are recoloured in a weak eosin solution (1 per cent. eosin 2·5 cm^3. to 100 cm^3. distilled water) for 2 or 3 hours. Granula stain badly by short eosin staining, even with strong solutions.

As the post-mortem alterations in the tissues, especially a strong kariolysis, occur much quicker in the organs of fowls than in mammals, it is of great importance that the pieces are fixed as soon as possible after death. If the point is to study the finer histological circumstances one should not wait for the death of the animal, but kill it in agony, to obtain pictures really of use.

Examination of the Blood

The blood tests are taken from the comb by cutting the end off one of the jags. When the comb has been made hyperemic beforehand by massage and washing in ether, sufficient blood is always obtained. The bleeding can be

stopped by cauterization. If this way is not successful, sufficient blood can always be obtained by puncturing the arm vein with a needle or a fine canula.

Hemoglobin tests can be executed by the aid of Sahli's hemometer. To obtain uniform figures it is necessary always to dilute with water after a certain time, *e.g.* 2 minutes. If it is put off longer the solution gets darker, and consequently higher figures are obtained.

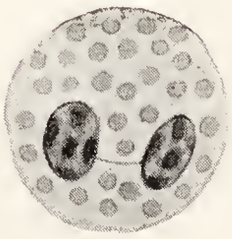
The counting of the blood-corpuscles as regards the red blood-corpuscles is carried out by the aid of a Thoma-Zeiss' or Bürker's counter. This method is not, however, practicable as regards the white ones, as the red corpuscles are nucleated, and therefore do not disappear in the ordinary solution of acetic acid. A circuitous method must, therefore, be used: first, the total number of red and white corpuscles must be determined in the counter, and then, in films, the ratio between the number of red and white blood-corpuscles must be determined. This is $\frac{1}{100}$ in normal animals. From the total number and this ratio the number of white corpuscles may then be found.

Staining of Films.—A little drop of blood is spread on an object-glass in the usual way, and this is moved to and fro in the air to obtain a quick drying and resulting good conservation of the blood-corpuscles. For staining I use a 0·3 per cent. solution of Leishman's dye in methyl alcohol. The preparation must first be fixed in the non-diluted dye. This liquid is poured away after the course of 2 minutes, and the dye, which is made of 1 part of the original methyl-alcoholic solution + 4 parts of distilled water, is added. (The mixing is done in a measuring glass.) After staining for 15 minutes, rinse in distilled water and leave the preparation in distilled water for 1 minute. Then it is blotted with filtering paper, dried well in the air, and finally embedded in damar-rosin in xylol.

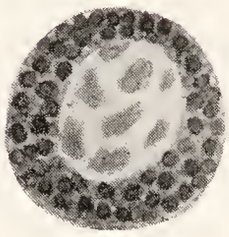
Erythrocyte.

Platelet.

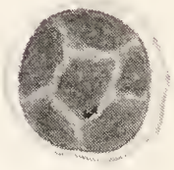
Polynuclear.



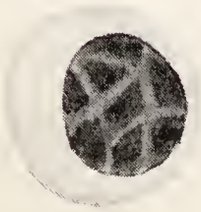
Polynuclear.



Mast-cell.



Lymphocyte.



Lymphocyte.

Lymphocyte.

Monocyte.

TEXT-FIG. 1.—CELL-FORMS OF NORMAL BLOOD.

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IV

BLOOD AND BLOOD-FORMING ORGANS IN NORMAL FOWLS

The Blood

HEMOGLOBIN.—When the content of hemoglobin is determined by Sahli's apparatus, a number is obtained for adult hens, which varies between 45 and 70, with an average of 56. The cocks reach a higher number, with an average of 72, the chickens a lower one, with an average of 45. In order to obtain values which may be compared, the dilution with water must always be made after a stated time, for instance 2 minutes.

The number of erythrocytes.—As an average of 6 determinations I have found 2,900,000 per mm^3. In cocks the number may at times rise still higher, up to 4,000,000.

The number of leucocytes is about 30,000.

The Morphology of the Blood

(Text-figure 1.)

The erythrocytes are oval, flat cells containing hemoglobin, with a narrow almost rod-shaped nucleus which stains very dark.

The leucocytes.—Here we re-find the same types as those known from man.

Differential count shows the following percentage distribution :

Polynuclears	rod-bearing	29 per cent.
	grain-bearing	4 „
Mast-cells		2 „
Monocytes		12 „
Lymphocytes		53 „

The polynuclear leucocytes comprise two different forms. The most ordinary form is a cell with dark, lobed nucleus and a protoplasm full of peculiar spindle-formed "granulations," which stain in eosin but not by Graham's oxydase reaction. These cells, which in number and function correspond to the neutrophilous polynuclears of man are considerably increased by hyperleucocytosis, for instance in tuberculosis. The other kind of polynuclears is to be found in much smaller number. They also have a lobed nucleus, but single lobes are bigger and lighter than in the first-mentioned group. The protoplasm contains coarse, round grains which stain in eosin, and give a positive reaction by Graham's oxydase-reaction.

The mast-cells which constitute a few per cent. correspond to the mast-cells in man. They have coarse granula which stain purple in Leishman's dye.

The monocytes are large cells with non-granular, blue-stained protoplasm and a great kidney-shaped nucleus. They resemble the monocytes of man.

The lymphocytes correspond completely to the lymphocytes of man. There are partly small forms with round, dark nucleus and narrow, pale protoplasm, partly larger forms with round or oblong nucleus and transparent, light blue, almost colourless protoplasm. The larger forms sometimes contain single red grains in the protoplasm.

Blood-platelets.—These are nucleated cells resembling the erythrocytes. The protoplasm does not contain hemoglobin but 1 or 2 azurophilous grains. The shape of the nucleus is oval, and it is a little larger than the nucleus of the erythrocytes. Blood-platelets are found in almost the same number as leucocytes.

The Blood-forming Organs

The bone-marrow.—The marrow in the long tubular bones is red also in the adult animals, the lower part of the tibia-marrow apart, which with advancing age changes into fat-marrow. The structure of the bone-marrow is very simple, as the tissue consists of solid balks that form a

Text-fig. 2.—Diagram of Normal Bone-Marrow.

The dark areas are the trabeculæ in which fat-cells are to be seen. The light areas are the sinuses which contain erythrocytes and erythroblasts.

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spongeous tissue whose cavities are occupied by large venous sinuses (Text-figure 2).

The trabeculæ consist almost entirely of close-set granulated cells : myelocytes. Groups of rod-bearing polynuclears are to be seen in smaller numbers. Furthermore sparse fat-cells are met with. The myelocytes with large central nucleus (" myelogonies ") multiply by mitotic division. In some of the daughter-cells the nucleus is smaller and darker, places itself eccentrically, and finally the granula develop into fusiform rods. Non-granular prephases (myeloblasts) are not found under normal conditions. The mitoses are always seen in the granulated cells. Lymphatic tissue is only seen in very small quantities in the trabeculæ, viz., as inconsiderable accumulations of small lymphocytes in the wall of the larger vessels.

The venous sinuses are thus placed in the spaces between the trabeculæ, and their wall only consists of a layer of flat endothelial cells. They are filled with blood. Besides mature erythrocytes, pre-phases may be found, *i.e.* partly erythroblasts with roundish, paler nucleus and hemoglobin-poor protoplasm, partly erythrogonies with large pale nucleus and narrow basophilous protoplasm. Mitoses are most frequently found in cells containing hemoglobin, in normal conditions erythrogonies are rather few in number.

The spleen is of a structure quite similar to that of the mammals (Plate I. Fig. 2). Trabecules, follicles and pulp tissue are consequently found. The follicles are irregularly bounded accumulations of lymphocytes round small arteries. Their diameter is about 400 μ. They contain small lymphocytes, but in young animals follicles with germ-centres are frequently met with. These measure about 80 μ in diameter, and consist of lymphoblasts. Mitoses are constantly found. The pulp tissue contains erythrocytes, small lymphocytes, polynuclear leucocytes, but no myelocytes.

The liver.—As in man there is normally no bounding between the single lobuli. The liver has no blood-forming function outside the life of the fœtus. It is, however, of interest for the understanding of the pathological condi-

tions that normally we find periportal accumulations of cells consisting of myelocytes and small lymphocytes. These two kinds of cells are not found intermixed, but in separated accumulations in the wall of the larger branches of the portal veins. The capillaries of the liver are normally empty, or contain a few erythrocytes.

The lymphatic apparatus of the intestine.—As O. Bang has shown, the mucous membrane contains lymphatic tissue, here and there with marked formation of follicles. Especially at the entrance to the blind gut great accumulations of lymphatic tissue, suggestive of the plaques of Peyer, are found. Also in the follicles of the gut I have been able to show germ-centres with plenty of mitoses.

Thymus.—The formations resembling lymphatic glands, which are situated on either side of the neck in a number of 4–6, on microscopical examination prove to be thymus, which in this way is divided into a series of small organs. The lymphatic glands are completely lacking in fowls. The same is the case with all other birds except ducks and geese.

Kidneys.—In the real kidney tissue small accumulations of lymphocytes are found here and there. Myelocytes are generally not seen, but on minute examination small accumulations of them may be detected. In the wall of the basin of the kidney, on the other hand, rather large accumulations of myelocytes and lymphocytes will be found.

Summary

The fowls like the mammals have as well myeloic as lymphatic tissue. The myeloic tissue is primarily to be found in the bone-marrow, in which the polynuclear cells are formed, but furthermore in small quantity also in the liver, in the wall of the basin of the kidney and even as traces in the real parenchyma of the kidney. Lymphatic tissue is found as spleen- and gut-follicles, in thymus, and in smaller quantity also in the liver, kidneys and other organs. Normally germ-centres are found in spleen- and gut-follicles. Lymphatic glands are entirely lacking.

V

THE VIRUS OF THE LEUCOSIS OF FOWLS

THOUGH it has from most quarters been admitted that the experiments with the leucosis of fowls deserve interest because they, to a certain extent, throw light on the leucemic diseases of man, at the same time objections have been raised to the interpretation of the experiments as well as to the conclusions of comparative pathologic kind which they have given rise to. Schridde thought that he could produce a leucemic blood-picture in healthy fowls by inoculating normal organs of hens. This result is at variance with all experience, but would not, even if it had not been wrong, be of the least importance for the question, because the leucosis of fowls does not only consist of changes in the blood. Skiba's objection that the experimental disease is not identical with the spontaneous leucemia of fowls, is of equally slight importance after the considerable evidence to the contrary now present. Burchardt's assertion that the leucosis of fowls must be an impaired tuberculosis, is so greatly at variance with all evidence as regards the two diseases, that it can hardly be taken in earnest. Besides, it has been directly disproved by an experiment by the author in which I, in a case of mixed infection of tuberculosis and leucosis, was able to separate the tubercle bacilli by filtration of the inoculation material, and obtain clean cases of leucosis in the inoculated animals. Folke Henschen's attempts at co-ordinating the leucosis of fowls with anemia pseudo-leucemia infantum is only very insufficiently proved, and for various reasons deceptive. As said before,

all these objections are no more of any great importance, and it is now generally admitted that the leucosis of fowls is a leucemia-like disease, and that it is transferable to healthy animals. On the other hand, there are varying opinions as to what importance the results gained may have for the understanding of the leucemia of mammiferous animals, and particularly of man.

Against the legitimacy of comparing the leucosis of man with that of fowls are partly adduced the scruples always felt in co-ordinating the diseases of two such distant species, partly the difference in the anatomic picture, such as it appeared after the original investigations into the leucosis of fowls. As the whole view of this disease is dependent on a thorough knowledge of the histological alterations, and of the histogenesis, I have in the first instance regarded a thorough revision of the histology of the leucosis of fowls as my main task, for which several series of inoculations have given me sufficient material. The results of those examinations I have previously reported. In the present work I shall further strengthen the system I have set up, and add an explanation to the points in the histogenesis which formerly were not clear.

Leucosis of fowls is met with rather often in stocks in Denmark, but it is also to be found in other places, and has thus been pointed out in Germany, Sweden and America. It is not rare to find several cases in one place, so that small epidemics or endemics may even be spoken of. As a rule it is anemia which draws attention to the disease. In the animals affected the comb is more or less yellowish-pale. They are not as active as the healthy fowls, and eat less. The examination of the blood shows anemia or leucemia. By post-mortem examination swelling of the liver and spleen is found, while the bone-marrow is of more greyish colour than normally. In other cases changes are found in the organs of animals which have died unexpectedly, without having been pale beforehand. In the following chapters I shall describe at greater length the

details of the clinical picture and the post-mortem findings.

If an emulsion of the organs is made by mixing them with a 0·9 per cent. solution of sodium chloride, and injecting this emulsion intravenously in a quantity of, *e.g.*, 1 cm^3. in a series of fowls, some of them will in the course of 3 to 4 months be taken ill with symptoms similar to those shown by the animals first attacked.

From these the disease may again be transferred to healthy animals, and in this way be propagated further as long as desired.

The original experiments, carried out by Ellermann & Oluf Bang, were later confirmed by Hirschfeld & Jacoby, Ellermann, Schmeisser, Magnusson. The number of transmissions in the experimental strains is shown in the table below :

TABLE III

Synopsis of Transmission Experiments

Writer.	Designation.	Number of Generations.
Ellermann & Bang .	Strain A.	6
,, ,, .	,, B.	1
,, ,, .	,, C.	2
Hirschfeld & Jacoby .		5
Ellermann . .	Strain D.	2
,, . .	,, E.	6
,, . .	,, F.	1
,, . .	,, G.	1
,, . .	,, H.	12
Schmeisser . .		5
Magnusson . .		1

The table shows that it is not a case of quite a few experiments, but that the transmission has succeeded in a considerable number of cases.

If now we examine what is the active principle in the emulsion of organs, there are three possibilities, which must be taken into consideration, viz. : (1) That it might be an unorganized virus ; (2) that it might be cells from the blood-forming organs, which have continued growing in

the new organism in the same way as cancer-cells which are transplanted; (3) that the emulsion might contain a microbe able to produce the disease.

The first possibility, the *poisoning*, can soon be rejected. In the first place, we have no knowledge of poisons which do not show their effect until several months after the administering of the poison. Secondly, the poison would soon be diluted to such an extent that there could be no question of any effect. If, *e.g.*, 1 cm^3. of blood is inoculated, which experience shows is sufficient to call forth the disease, and if the total quantity of blood in the fowl is calculated at 50 cm^3., we have immediately a dilution of the poison in the ratio of 1 to 500, in the second generation a dilution in the ratio of 1 to 250,000, and in the twelfth generation the dilution will have to be expressed in a number written in 33 digits! In these calculations I have temporarily taken it for granted that the hypothetic poison was retained in the blood of the inoculated animal. This is, however, at variance with all experience, as poison in the blood is bound or excreted. Therefore it is quite inconceivable that an unorganized virus should be able to call forth the disease. The transmission can only be explained by an agency capable of multiplication, either cells or microbes. It is now easy to show that it is not a case of the *transplantation of cells*. For if the emulsion used for inoculation is filtered through a Berkefeld filter, one gets a fluid without cells, which produces the disease just like the unfiltered emulsion. After this we have no choice but to suppose an *infection*. The Berkefeld filters are, however, so fine that they retain not only cells, but also microbes. Therefore there cannot be any question of an infection with microbes of the size of bacteria, the virus of the leucosis of fowls must belong to the group of filterable microbes. Consequently, they are micro-organisms which are just on the border of the visible or below this, and the presence of which is only perceptible by the morbid changes they produce. It is in harmony with this that neither by direct microscopic

investigation nor by cultivation has it been possible to demonstrate microbes in the organs of the leucemic animals.

The first filtering experiments, altogether 3, were made in 1908 by Oluf Bang and myself, and I have subsequently confirmed the correctness of the positive result by 3 other experiments. As the filtration experiments are of the greatest importance to the understanding of the disease, and as there are only very few at present, I shall here quite briefly report all the experiments made.

Berkefeld Filtration

First Experiment (3/11/1907).—By centrifugation of emulsion of organs from hen 161 an unclear, virtually cell-free fluid was obtained which was filtered through a Berkefeld candle, No. 12. 10 cm^3. of the filtrate, which was completely clear, was intravenously inoculated into each of 5 normal hens ; the result was that 3 of these (Nos. 251, 257, 259) contracted the disease.

Second Experiment (17/1/1908).—Emulsion of organs deriving from 2 fowls suffering from leucemia (Nos. 113 and 236) was similarly centrifugated and filtered. The filtrate was clear, and on microscopical examination after centrifugation found to be entirely without cells. Five cm^3. of this was intravenously inoculated into each of 5 normal hens. One of these (No. 77) contracted the disease.

Third Experiment (20/2/1908).—For this experiment was employed an emulsion of organs from an animal suffering from leucemia (No. 232) in a copious supply of 0·9 per cent. NaCl solution (15 : 350). The emulsion was centrifugated for 10 minutes in a rapid separator (4000 rotations a minute). The opalizing fluid was carefully taken up in a pipette and was filtered through a Berkefeld candle, No. 11, after which the clear filtrate was injected intravenously into 6 normal hens. One of these animals (No. 70) contracted a typical leucemia.

Fourth Experiment (7/12/1912).—Twenty grms. of liver

and spleen from a spontaneous case of leucemia (hen E) were mixed with 100 cm³. of 0·9 per cent. NaCl solution. The emulsion was centrifugated for 5 minutes with a rapidity of 2500 rotations a minute. Fifty cm³. of the fluid was taken up in a pipette and diluted with 0·9 per cent. NaCl solution to make 90 cm³. The content of albumin was now 0·4 per cent. (Walbum). The fluid was filtered through a Berkefeld candle, No. 12, by which in the course of 3 hours 40 cm³. quite clear filtrate was gained, which proved sterile by seed on agar and broth. It was intravenously injected into 8 healthy animals, each of them receiving 3 cm³. Of these animals only one (N.S., No. 41) contracted the disease.

Fifth experiment (5/7/1917).—For this experiment was employed leucemical organs from hen N.S.,No. 176 (strain H). Fifteen grms. of the organs (liver, spleen and bone-marrow) were mixed with 0·9 per cent. NaCl solution. The emulsion was filtered through cotton and diluted to make 100 cm³. This fluid was passed through a Berkefeld candle, No. 12. The filtrate was quite clear and gave no growth on agar and broth, while the control grafting from the unfiltered emulsion gave rise to a rich growth. The filtrate was intravenously inoculated in doses of 1 cm³. into 10 normal animals. Two of these (Nos. 211 and 212) contracted the disease.

Sixth experiment (27/3/1918).—Emulsion of organs from leucemic hen, N.S., No. 271, was filtered through a Berkefeld candle, No. 12, and was injected in doses of 1 cm³. into each of 8 healthy animals.

None of these contracted the disease.

Reichel Filtration

First experiment.—The experimental material consisted of organs from hen N.S., No. 7, which besides being leucemic was also suffering from tuberculosis.

Emulsion of spleen, bone-marrow and kidney-tissue in a 0·9 per cent. NaCl solution was centrifugated for 5 minutes

(2000 rotations in a minute) by which an unclear, reddish fluid was obtained which was passed through a china filter (Reichel). The filter was previously made sterile by boiling an hour. Twenty-two cm^3. of crystalline fluid was obtained, which gave no growth on agar and broth. The filtrate was intravenously injected into 10 normal hens, each one receiving 2 cm^3. Two of the animals (N.S., Nos. 22 and 24) contracted a typical leucosis, and none of the animals developed tuberculosis. A separation of the virus of the leucosis from the tubercle bacilli had thus been effected by the filtration.

Second Experiment.—Emulsion of organs from the above-mentioned No. 24, and the same method as in the other cases was employed. None of the 10 inoculated animals were attacked by the disease.

Third Experiment.—Emulsion N.S. 71. Result negative.

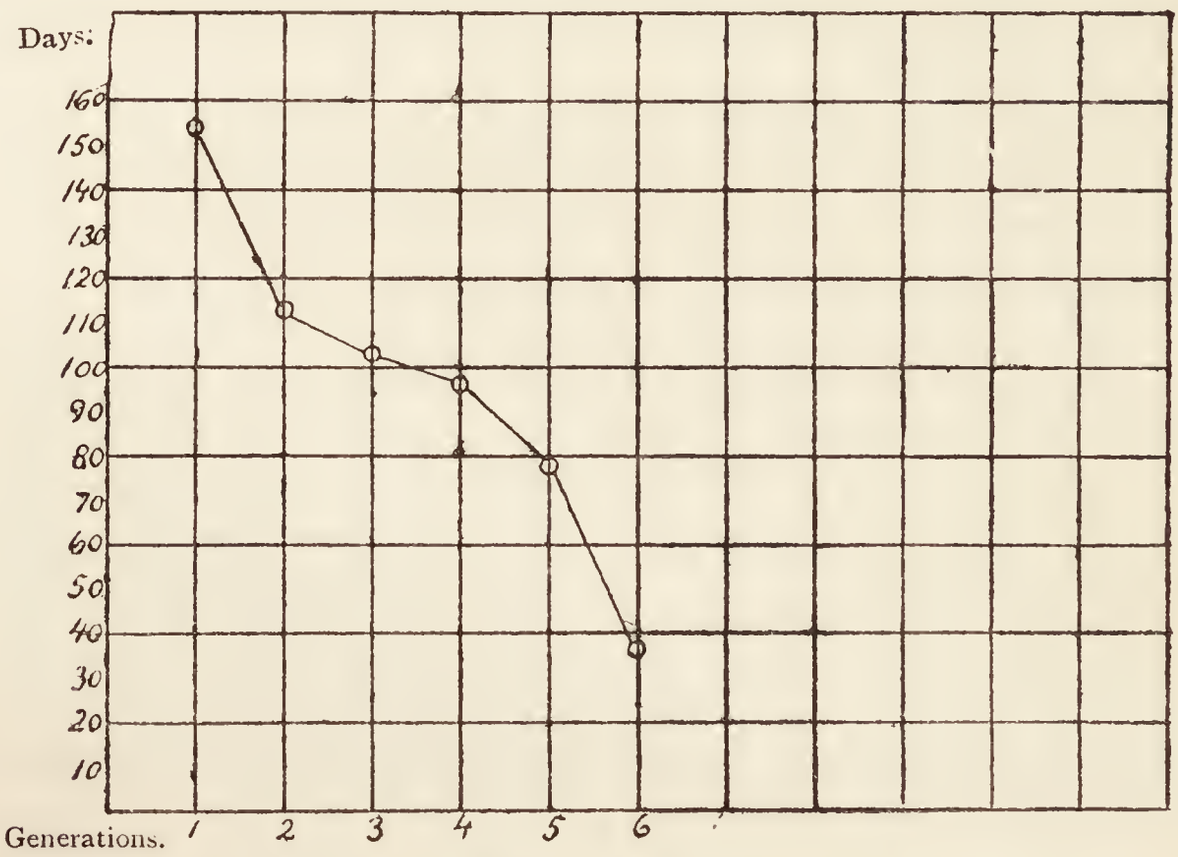
The result of all the filtration experiments is that the virus of the leucosis regularly passes through the Berkefeld filters (5 out of 6 experiments), and sometimes through the Reichel filtres too (1 out of 3 experiments). The filtrates were always quite clear as crystal, and proved sterile by seed on agar and broth, while control grafting from the unfiltered emulsion gave rise to a rich growth of bacteria on the same substrates (note especially Berkefeld experiment, Nos. 4 and 5).

Apart from the fact of their passing through the filter, which thus indicates the minuteness of the microbes, we only know very little about the properties of virus. The durability, according to the very few experiments made, seems to be rather limited (few days), even if the material is kept at a low temperature. The place of inoculation is of importance, since the disease can be called forth by intravenous, intraperitoneal and intramuscular inoculation ; while, on the contrary, inoculation in the subcutaneous tissue is ineffective.

It is of greater interest that by continued inoculation it can be observed how the virus gradually gets stronger. This increase of virulence is shown by the

fact that the course is shorter for every generation of inoculation.

The curve below shows the alteration in the duration of the disease in the course of the inoculations with the strain E of the present writer. On the vertical axis is marked out the number of days, on the horizontal axis the number of generations. The duration is reckoned from the inoculation to the death of the animal. The figures given are averages of the duration of the different



TEXT-FIGURE 3.—CURVE SHOWING THE DURATION OF THE DISEASE WITH STRAIN E.

cases in each generation. It shows that the average duration in the first generation is about 5 months, in the second generation hardly 4 months, and that it constantly decreases until in the sixth generation it is only a good month. The experiments of the duration in strain H have given a quite similar result, only the fall is here slower. In the first generation the duration was more than $4\frac{1}{2}$ months, but the course got constantly shorter, and was in the ninth generation only a good month. A third strain (strain D) comprised only two experimental generations,

but showed a similar course, the duration being a little more than 5 months in the first generation and less than 7 months in the second generation.

It will be observed that the conditions are very much like those of another "filterable" virus, viz., that of hydrophobia. If a rabbit is inoculated intracerebrally with spinal marrow from a dog suffering from rabies (*virus de rue*, Pasteur), 2 to 3 weeks pass from the day of the inoculation to the outbreak of the disease. If now further inoculation is made on rabbits, the period of incubation

TABLE IV

Synopsis of Percentage of Takes in Experiments undertaken by various Authors

	Number of Animals inoculated.	Number of Animals attacked.	Takes.
Ellermann & O. Bang (Strain A, B and C)	83	34	41 per cent.
Hirschfeld & Jacoby . .	49	22	45 ,,
Ellermann (Strain E) . .	79	17	22 ,,
Schmeisser	40	13	33 ,,
Ellermann (Strain F, G and H)	136	36	26 ,,
	387	122	32 per cent.

will constantly decrease, until it has gone down to 7 days, at which point it will remain (*virus fixe*).

Transferring these terms to the leucosis of fowls we have consequently, with the spontaneous virus, a total duration of the disease of 4 to 5 months, and with *virus fixe*, a duration of about 1 month.

Of what the virulence in itself consists the experiments do not tell us anything about. Perhaps it is due to an increased velocity of reproduction of the microbes as Krauss fancied in the case of hydrophobia, or to an increased production of poison (Schüder), or to a greater power of resistance in the means of defence of the experimental animal, or perhaps to something quite

different. Whether it is the one or the other, it is at all events without influence on the number of animals affected.

It was seen in the original experiments, and it is a fact which has subsequently been corroborated over and over again, that only a minority of the inoculated animals were taken ill. The percentage results of the different researches are seen in the preceding comparison.

It appears that of the animals inoculated only 32 per cent. are attacked. The majority of the animals, 68 per cent., are in possession of a natural resisting power. Hence the infection with leucosis is not only dependent on the "exogenous factor," viz., the introduced virus; but to make the disease develop a disposition in the experimental animal is furthermore required. Individual differences in regard to resistance to infections are known from other infectious diseases; but nothing is known about the causes of it. Is resistance to leucosis due to a constitutional disposition, or do exogenous influences come into play? The explanation that the resistant animals had acquired immunity in consequence of an earlier attack of the disease, from which they had recovered, seemed obvious. To this may be objected that the disease is nearly always fatal, and further that resisting power is no permanent quality. For it is seen that, by repeated inoculations, it may be possible to infect animals, which were immune by the first treatment.

A knowledge of the natural resisting power is important if we want to be able to count on a positive result of the ordinary transmissions, and to draw conclusions from experiments with negative results.

It is evident that, when only a few animals are inoculated, a negative result is just as likely as a positive result, since two-thirds of the animals are immune. If the probability of the inoculation taking is calculated with a different number of inoculated animals in the experiment, the result will be as follows:

TABLE V

Number of positive Experiments by various Numbers of Animals inoculated

Number of Animals in the Experiment.	Positive Result.	
	Calculated.	Found.
5	74 per cent.	87 per cent.
8	89 ,,	89 ,,
10	92 ,,	100 ,,
12	97 ,,	100 ,,

This shows that the prospect of a positive result, when inoculating 5 animals, is 74 per cent. Thus in one-fourth of the experiments the inoculation will not take, even if the inoculation material is quite active. If 8 animals at a time are inoculated, the result will in the 9 out of 10 cases be positive, and by using 12 animals one may be almost sure of obtaining positive results, since it will only happen 3 times out of 100 experiments that the inoculation fails to take. For economical reasons I have generally worked with 8 animals at a time, but to ensure success, or in the case of experiments with negative results, it is necessary to increase the number.

It is evident that the number of animals attacked in the individual experiments will depend on how many among them chance to be liable. Inoculating, *e.g.*, 8 animals, the number infected may range from 1 to 6. Hence a high percentage of successful inoculations may be due solely to accidental circumstances, and is not, as one might feel inclined to believe, connected with any special virulence of the inoculation material. For it is seen that the percentage of taking in the individual generations oscillates quite irregularly, at the same time as the virulence, measured by duration of the disease, gradually increases. An augmentation of virulence, therefore, does not involve any augmentation of the percentage result. The natural

resistance will still protect the majority of the animals against the infection.

If we view the communications about homologous inoculations present in the literature in the light of these experiences, it is evident how very little importance can be attributed to them. As a rule only a few animals have been used for inoculation, and even Lüdke, who made his experiments on dogs *after* the publication of the positive experiments on fowls, and whose results at best were dubious, used only 5 animals. An exception is formed only by Haaland's experiments on mice, in which more than 100 animals were used. As now fowls, which according to clinical experience (frequent endemic occurrence) are the animals which are most susceptible to the leucemic infection, nevertheless show such a considerable resistance, a similar resistance or possibly a still greater one must be supposed in other species of animals. Therefore it is as likely as not that a still larger number of animals must be employed than in the experiments on fowls, to get the prospect of a positive result. How large this number will have to be it is of course, for the time being, impossible to say.

VI

THE LYMPHATIC LEUCOSIS

IN this form of leucosis one finds only extravascular hyperplasias, while the blood-change is generally lacking. Clinically the disease gives no symptoms ; but death occurs rather unexpectedly. Therefore the length of the incubation period is impossible to determine. The examination of the blood shows a normal hemoglobin number and blood picture. In a few cases, however, in consequence of the bone-marrow being attacked, an anemia may develop a short time before death. Leucemia, on the contrary, is not seen, at any rate I have not hitherto met with any leucemic case, although I have in the course of time examined a considerable number of spontaneous as well as experimental cases.

On autopsy is found a peculiar picture which generally makes it possible immediately to know the disease from the myeloic or the intravascular lymphoid form. The liver is commonly very much enlarged, up to 8 times its normal weight. It is strown with whitish spots up to the size of a pea and they are often a little raised. Less frequently the surface may be quite homogeneous, viz., when the new-formed tissue is more equally spread. The spleen is enlarged, but to a much less degree than in the liver. Its colour is most frequently very pale, caused by the displacement of the pulp tissue. On the surface, as well as on the cut surface, marked design of follicles may often be seen with the naked eye. The kidneys frequently present a similar mottled aspect to the liver, so that areas with normal kidney tissue alternate with smaller or greater

white areas. The bone-marrow is generally of normal dark red colour; now and then, however, small white spots are met with, and in certain cases it may be quite greyish. Of other organs which are frequently attacked, thymus, intestine and peritoneum must be mentioned.

The characteristic features in the post-mortem findings are thus partly the mottled aspect of the organs, which is due to the heterogeneous, often nodule-shaped development, partly the severe swelling of the liver and the, in comparison with this, less pronounced swelling of the spleen.

The microscopical examination shows that the alterations are due to a hyperplasia of the lymphatic tissue, normally occurring in the various organs (spleen, liver, intestine, thymus, kidney, etc.), and that other pathological processes are lacking. While the normal lymphatic tissue consists of typical small lymphocytes, apart from the germinal centres which contain larger cells, lymphoblasts, the new formed lymphatic tissue is composed of large and medium-sized cells, which are often in mitotic division. In the leucosis, therefore, there is a lymphoblastic hyperplasia. It must, however, be emphasized that the lymphoblasts are pathologic and differ by their considerable size, stronger colouring, and coarser chromatin structure from the lymphoblasts normally occurring in the germinal centres. These cells have a roundish or more irregular form. The nucleus is comparatively large, roundish or oval, with large, dark nucleolus and coarse chromatin grains. The protoplasm is fairly narrow, and is commonly, to some extent, stainable in hematoxylin. These cells differ by their stronger colouring from the myeloic cells, and by their less regular form from the lymphoidocytes (*vide* pp. 79–80). In fairly thin sections it will be seen that the lymphoblastic tissue has another peculiarity which characterizes it in contradistinction to the myeloic tissue in the fowls, this, viz., that the individual cells are not interconnected, and that they are found to be imbedded in a network of fine threads of connective tissue (reticulum). Sometimes areas

are found which, owing to their particularly strong colour, form a contrast to the remaining hyperplastic tissue. In the liver, for instance, it is seen that some few of the hyperplastic follicles are much darker than all the others. The phenomenon is not unknown in human pathology, and may be met with in ordinary inflammation hyperplasias of lymphatic tissue, particularly in the lymphatic glands. Possibly it depends on the age of the cells.

Viewing the hyperplastic tissue in the lymphatic leucosis, it is not immediately evident that we are really dealing with lymphocytes and lymphoblasts. In the different forms of the leucosis of fowls at least three different cell-forms resembling lymphocytes, consequently "lymphoid" cells, may appear, viz.: (1) real lymphoblasts, (2) myeloblasts and (3) lymphoidocytes. The two last-mentioned forms of cells will later on be thoroughly elucidated. I have already mentioned certain features which characterize the lymphatic cells here in question. These are, however, not so certain and palpable that they allow of a distinction in all circumstances, and at any rate the lymphatic character of the cells must be proved. In the lymphatic leucemia of man this does not generally cause any trouble. Here we have partly the severe hyperplasia of the lymphatic glands, partly the fact that the new-formed cells as well in the tissues as in the blood are frequently typical small lymphocytes. None of these things are applicable to the fowls. In the first place, lymphatic glands are entirely lacking in these animals; in the second place, the hyperplasia is always large-celled, lymphoblastic. The only way to go, therefore, is to investigate the histogenesis, so as to try directly to make out from which tissue elements the hyperplasia originates. For this purpose the spleen is the best suited organ. In not too much advanced cases it may be proved that the hyperplasia originates in the follicles, while the pulp tissue is passive and is forced aside. In the liver the picture is not so convincing, the finding of normal small accumulations of myelocytes next to the new-formed tissue in the periportal

connective tissue, however, tells against the myeloic origin of the hyperplasia. When further is added that the tissue of the bone-marrow, as well the myeloic as the erythropoetic, in several cases is quite normal, one must be justified in regarding the lymphatic nature of the hyperplasia as positively established.

In the *liver* the hyperplasia is situated in the periportal connective tissue (Plate I. Fig. 1), and the picture in the first stages quite resembles that which is known from the lymphatic leucosis of man. Most frequently, however, there is a tendency to uneven growth and confluence of the single infiltrations to smaller or larger nodules. In these liver tissue is completely lacking, or is only to be seen as quite narrow bands.

In the *spleen*, in the most advanced cases, a homogeneous mass of lymphatical tissue is found, in which it is impossible to distinguish follicles and pulp.

Before entering on the details of the histologic picture it is necessary quite briefly to touch on the conditions in the normal spleen. In this the pulp tissue takes up the greatest area and is seen as broad bands between the lymphatic follicles. The latter are of irregular shape, often toothed, and not distinctly bounded (Plate I. Fig. 2), and they measure about 300 μ in diameter. They consist of small lymphocytes, but frequently a secondary follicle is to be seen in their interior (germinal centre), a regular, circular accumulation of cells of about 80 μ in diameter, paler than the rest of the follicle and containing large cells, —lymphoblasts. The germinal centres always contain mitoses.

In the lymphatic leucosis it is the follicles that dominate the picture (Plate I. Fig. 3). They differ from the normal follicles by their considerable size, dense placing and regular, roundish shape. They often measure 500 to 600 μ in diameter, and the pulp tissue forms narrow bands in between them. Further examination shows that they consist of nothing but large and medium-sized lymphatic cells with many mitoses (Plate I. Fig. 4). A distinction between

primary and secondary follicle is not found. These follicles, owing to the size of the cells and the numerous mitoses, most of all remind one of very much enlarged germinal centres, only as mentioned, the cells differ in appearance from the normal lymphoblasts. In the *kidneys* the hyperplasia is often dispersed in spots. In certain places the tissue is quite normal, in others it is seen how the renal tubules are forced from each other by the new-formed tissue (Plate I. Fig. 5). Thus as a final stage we find large connected masses of new-formed tissue in which the renal tubules are quite lacking.

The *bone-marrow*, too, in several cases appears microscopically normal. In many cases, however, scattered accumulations of lymphatic cells are met with, which have probably developed from the very scarce accumulations of lymphocytes that under normal conditions are to be found in the marrow, and in certain cases the myeloic tissue may be more or less displaced.

In other organs as thymus, intestine and skin microscopy shows conditions similar to those described above. As an example of lymphatic leucosis I shall report the following cases :

CASE I

Hen N.S. 341.—Inoculated on April 1, 1919, with blood from 335. On April 24, 1919 : Pale for some days ; dead at 2 o'clock. Blood preparation from the arm vein shows : some erythroblasts, scarce lymphoidocytes. No augmentation of leucocytes. Weight of animal, 1150 grms.

Autopsy.—*Liver* very much enlarged ; weight, 120 grms. Surface reddish, without white spots.

Spleen of normal colour and of almost normal size ; weight, 3·2 grms. On surface as well as on cut surface fine white spots, irregularly dispersed, are seen.

The *kidneys* are enlarged, sown with white spots, consisting of nodules up to the size of a hemp-seed. In certain places the tissue is to a great extent quite white and soft. Weight of right kidney, 20 grms. In the mucous membrane of the small intestines a single nodule the size of a hemp-seed. Some similar ones in the blind gut.

Heart, *lungs*, *thymus*, *skin* and *bones* normal.

Microscopy.—*Liver*.—Numerous medium-sized periportal cell

infiltrations, consisting of round non-granular cells with large dark-coloured nucleus and rather narrow protoplasm, are to be seen. Moreover, there are some intra-acineous infiltrations with similar cells which force the trabeculæ of the liver-cells from each other. Now and then capillaries that only contain erythrocytes are met with.

Spleen.—Large, well-limited follicles, that measure about 400 μ in diameter and consist of large lymphocytes are to be seen everywhere. Mitoses are often met with in these cells, which are of the same appearance as the cells in the liver. In the pulp tissue mostly erythrocytes.

Kidneys.—The tissue is in spots quite normal. In some places a slight interstitial infiltration, in others only newly-formed lymphatic tissue, which encloses scattered renal tubules.

Intestine.—The nodule consists partly of lymphoblasts, partly of small lymphocytes. The lymph spaces in muscularis are crowded with large lymphatic cells.

Bone-marrow.—Few fat cells. Myeloic tissue very scanty. In a few places remnants of trabeculæ with "small dark cells." Sinus are narrow, contain almost only erythrocytes. The tissue consists essentially of non-granular dark cells of the same type as in the infiltrations in the other organs. Dispersed in the tissue some giant cells.

The picture is on the whole very typical. The liver certainly shows a uniform surface; but, on the other hand, the follicle design in the spleen is distinct, and the kidneys are full of white infiltrations. The microscopical picture is also remarkably typical. In the liver tissue the infiltrations are quite regularly dispersed, and almost all of the same size. Besides the ordinary periportal infiltration there is also a considerable intra-acineous lymphatic infiltration. This is the reason why cut surface as well as surface is plain, not spotted. In the spleen one very large follicle is seen beside the other, all of them consisting of lymphoblasts in lively propagation. The process in these organs has the pronounced character of a system affection.

CASE II

Hen N.S. 75.—On May 21, 1913, intravenously inoculated with 1 cm^3. of blood emulsion 59. Hb. 45. Blood preparation normal.

Dead on September 30, 1913. Has not been pale recently. Blood preparation shows : No augmentation of leucocytes, scarce myelocytes and mitoses.

AUTOPSY.—*Liver.*—Very large ; weight, 186 grms. ; colour, dark red, with dense white spots up to the size of a hemp-seed.

Spleen.—Of about normal size ; weight, 4 grms.

Bone-marrow.—In tibia of dark red colour, the consistence firm, on the whole of normal aspect, but in various places small limited white nodules of about 500 μ in diameter are found.

Intestine.—Macroscopically nothing abnormal is found.

MICROSCOPY.—In the *liver* is found a tissue consisting of large roundish cells with narrow protoplasm. These cells are often in mitotic division. The new-formed tissue forces aside the liver tissue, so that it forms rather narrow bands. The capillaries, which are practically only to be found in the real liver tissue, are empty or full of erythrocytes. Myelocytes in small groups are rarely met with.

The *spleen* presents a distinct picture, as it is easy to distinguish pulp from follicle. The follicles are a little larger than normal, while the pulp tissue is rather diminished. The follicles only consist of medium-sized and large non-granular cells with a large nucleus which nearly fills out the whole cell body. In pulp many erythrocytes, fewer mononuclear leucocytes are found. Nowhere myelocytes.

Bone-marrow.—The structure of the red part of the bone-marrow is quite normal, as the blood-spaces contain erythrocytes, while myelocytes and rod-bearing polynuclears are found in the trabeculæ. The white nodules consist of large cells, like the cells in the other organs, and they are embedded in a fine reticular stroma. Mitoses are numerous. Besides the nodules, vessels which only contain erythrocytes are found, for which reason it looks as if the nodules were extravascularly deposited.

Intestine.—In colon considerable accumulations of large round cells are seen in spots, as in the other organs. Furthermore, it is seen that similar cells fill up the lymph-spaces in muscularis and extend towards the mesentery. In the small intestine and in the blind guts I have found no infiltrations of this kind.

In this case we find that the liver presents the typical picture with a considerable enlargement and many white spots. The bone-marrow contains some little white grains. Besides, its colour is normal. The microscopical picture of the organs is quite corresponding to that found in Case I.

Lymphatic Cases with Tumour-like Character (Leukosarcomatosis)

It has previously been mentioned that the lymphatic hyperplasias show a varying energy of growth within the same organ, so that in some places, for instance in the liver or in the kidney, macroscopically visible nodules appear. This tumour-like growth may in certain cases be particularly marked. For my treatise formerly mentioned, I have described such a case (N.S. 66) in which in an otherwise normal liver a tumour was found of the size of a nut, consisting of lymphatic tissue, while there was a hyperplasia of the follicles in the spleen. I have subsequently had the opportunity of examining three cases of this kind. They were mutually alike, and in all of them the hyperplasia had a more tumour-like character than usual. I shall here state two of these cases:

CASE III

Original Hen G.—On December 22, 1916, sent from Professor Hansen, who had received the animal from a place where several fowls had died.

Autopsy.—*Liver* very large; weight, 213 grms. The surface shows a mottled picture as closely placed whitish spots, and nodules are seen in the brown liver tissue, from very small up to the size of a nut. Also two nodules of the size of a walnut, one on the front, another on the back, both with slightly lowered central part. The cut surface presents a similar picture with partly sharply limited, partly less distinctly defined, nodules. The *spleen* is slightly enlarged; weight, 4 grms.; colour, pale yellowish-red.

Kidneys without nodules; colour, brown; weight of right kidney, 6·5 grms. In the upper part of the *small intestine* are revealed four yellowish-white nodules below mucosa, their size varying from the size of a hemp-seed to the size of a pea; in *rectum* is found three similar nodules, only a little smaller. In the one blind gut a similar one, the size of a hemp-seed. In the *mesentery* numerous closely placed roundish or oval nodules, the size of the head of a pin. Similar nodules on the surface of the *intestine*. Behind *rectum* is a roundish, slightly hunched tumour, the size of a hen's egg, which presses the cloaca in front. It does not adhere to the wall of pelvis. The lobes of thymus are a little enlarged.

Heart and *lungs* normal. No nodules in *skin*. *Bones* normal.

Microscopy.—*Liver.*—Numerous medium-sized or large periportal cell infiltrations are met with ; they consist of large non-granular cells, which are separated from each other and embedded in a fine reticular stroma. Their nucleus is roundish or oval ; the protoplasm rather narrow ; the periportal infiltrations have in several places combined and form great masses, in which no liver-cells or only quite narrow bands are found. The infiltrations have in several places grown into the acini between the trabeculæ of the liver-cells. The liver-cells are otherwise normal. The capillaries are not dilated. In the large vessels almost only erythrocytes are to be seen. Myelocytes are met with nowhere.

Spleen.—Numerous large follicles are to be seen, 500 to 600 μ in diameter, sharply delineated against the surroundings. They contain large and medium-sized lymphocytes. In the pulp tissue, which is reduced in extent, are erythrocytes, small lymphocytes, scarce large lymphocytes and no myeloblasts.

Bone-marrow.—The picture is in most places normal. Plenty of myelocytes in trabeculæ. Erythrocytes in sinus also normal. In a few places limited small accumulations of large, dark-coloured non-granular cells of the same type as those in the liver nodules.

Kidney.—In a few places in corticalis quite small, roundish accumulations of large lymphatic cells are to be seen. The tissue is otherwise natural. Myelocytes are not found. The vessels only contain erythrocytes.

Intestine.—The periportal as well as the submucous nodules consist of large lymphatic cells ; in muscularis too, corresponding to the submucous nodule, there are bands of large lymphocytes.

Retrorectal tumour.—The tissue consists of large round cells like those in the other organs. They are embedded in a distinct reticulum of fine threads.

CASE IV

Cockerel N.S. 191.—On December 22, 1916, intravenously inoculated with 1 cm^3. emulsion St. G. (Case III.) Hb. 60. On December 24, 1917, dead.

Autopsy.—*Liver* somewhat enlarged ; weight, 63 grms. ; colour, reddish-brown. On the surface is seen a score of whitish nodules, of size from a hemp-seed to a pea ; they are often to be seen on the cut surface.

Spleen small ; colour, reddish. Towards the top a nodule, the size of a hemp-seed, is seen in the surface. On the cut surface a distinct design of large follicle is seen.

The *kidneys* are very much enlarged. Weight of right kidney, 14 grms. They are quite penetrated by closely set white nodules, of size from a hemp-seed to a pea.

Bone-marrow.—In tibia the bone-marrow is dark red, white nodules are not met with. In both of the lungs some white nodules, the size of a hemp-seed. In the *skin* on the breast, a hemp-seed sized nodule. In the *mesentery* some hemp-seed sized nodules. On the surface of the intestine in its whole length, but most pronounced on colon and blind gut, are found some nodules up to the size of a pea. Behind *rectum* a nut-sized, rather firm tumour, which does not adhere to the skeleton. On left wing, corresponding to the wrist, a nut-sized tumour. *Thymus* not enlarged.

Microscopy.—*Liver.*—Round the portal branches is everywhere seen small or medium-sized lymphocyte infiltrations. The capillaries are empty. The fine nodules consist of a fine reticular stroma with embedded, large, non-granular, roundish cells. Liver-cells are in these parts seen only in few places, and only as narrow bands.

Spleen.—Numerous large follicles, measuring about 400 μ in diameter, and consisting of large and medium-sized lymphocytes, are found. The pulp tissue forms rather narrow bands between the enlarged follicles and contains numerous erythrocytes.

Kidneys.—The kidney tissue between the nodules is normal. The nodules consist of large and medium-sized lymphatic cells, interstitially placed and quite displacing the kidney tissue. Some few renal tubules are also seen between the lymphocytes. Myelocytes are nowhere to be found.

Bone-marrow.—The tissue is of a gelatinous character with rather few myelocytes. No lymphatic tissue. In sinus only erythrocytes.

Retrorectal tumour.—The tissue is connective tissue in which there are large accumulations of lymphatic cells, especially round the vessels. Some parts are only connective tissue, others, on the contrary, only lymphatic tissue.

Lung.—A nodule shows quite the same structure as those in the other organs.

From what has been previously said, it is unquestionable that we are dealing with lymphatic cases. As well the localization of the hyperplasia as the finer structure shows this. The two cases resemble each other to a striking degree. Besides the large parenchymatous organs being attacked, nodules are found in peritoneum (Cases III. and IV.), in the lung (Case IV.), in the skin (Case IV.), and especially large tumour-like nodules in the retroperitoneal tissue (Cases III. and IV.). We are thus dealing with cases of leucosis with a certain tumour-like

character, a sarcoleucosis (Hirschfeld) or a leucosarcomatosis (Sternberg). As mentioned, it was Sternberg's idea to divide the lymphatic leucosis of man in two forms, the real lymphatic leucosis and the leucosarcomatosis, which should be characterized by the hyperplasia being large-celled, and showing a tendency to tumour-like growth. Sternberg's view is correct as far as the large-celled forms of lymphatic leucosis often show a tendency to form tumours; but in reality we cannot sharply distinguish between the common leucosis and the leucosarcomatosis, since small-celled cases of leucosis, combined with tumour formation, may be found, and conversely large-celled cases in which this is lacking. Most pathologists, therefore, are disinclined to admit the distinction, but consider the common leucosis and leucosarcomatosis as manifestations of one and the same pathologic process.

If we look at the lymphatic form of the leucosis of fowls, we meet with the peculiarity that the hyperplasia, as it seems, is always large-celled. A gradual transition from ordinary cases to cases of tumour-like character is found. The classification of the tumour-like cases as a special form, leucosarcomatosis, is therefore chiefly of morphological interest, but has hardly any importance in regard to an etiological distinction. In favour of the latter is partly the appearance of tumour-like cases in strain E, partly the experiences with strain C, in which the inoculation with organs from a case of lymphatic leucosis with tumour formation, produced cases of the intravascular lymphoid type.

VII

THE MYELOIC LEUCOSIS

IN this type of leucosis, leucemic as well as aleucemic cases are known. In the leucemic cases the disease may take the following course: at the beginning the animal is less active and the comb is a little pale. Examination of the blood shows a slight reduction of the hemoglobin percentage, and in dry preparation of the blood only few abnormal cells are found: erythroblasts, myelocytes and lymphoidocytes. This stage may at times be of rather long duration, thus in Case III., in which it lasted 3 months. In other cases it is lacking, or is at any rate so transitory that already at the first examination leucemia in full development may be demonstrated. Like other changes in the blood of fowls (anemia, regeneration), leucemia often begins quite suddenly. The number of leucocytes is considerable (200,000 to 600,000), and the blood picture shows a pronounced myeloic character (Plate II. Fig. 1). Thus the following percentage composition may be found:

	Per cent.	Actual Numbers per mm³.
Polynuclears . . .	2	12,000
Myelocytes . . .	21	126,000
Large Mononuclears and Poikilonuclears . .	67	402,000
Lymphocytes . . .	5	30,000
Lymphoidocytes . .	5	30,000
	100	600,000

As regards the individual kinds of cells I shall offer the following remarks:

The *polynuclear leucocytes* constitute only a few per cent.; but, if the absolute number is calculated, it appears that this is 12,000 per mm^3., *i.e.* a value which may be regarded as normal. Thus there is ordinarily no question of an augmentation of the polynuclears, as it is found in the myeloic leucemia of man. Besides, the polynuclear leucocytes in myeloic leucemia are similar to those which are met with in normal blood; in several cases, however, they are in so far pathological as the granulation is produced, not by the normal long spindle-shaped elements, but by round or oval grains.

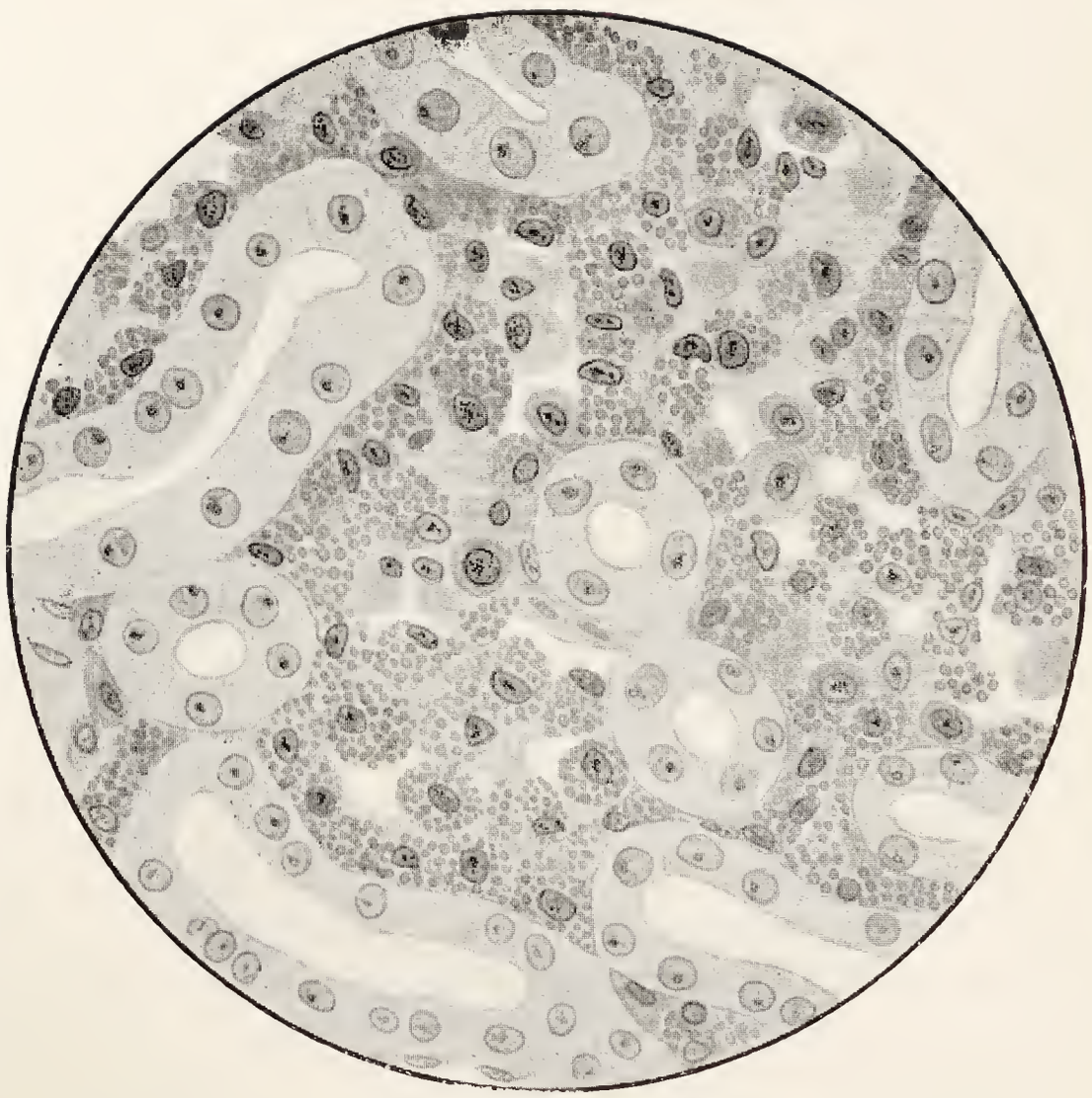
The *myelocytes* are big mononuclear cells with a round or oblong nucleus. This is centrally or eccentrically situated, and in the latter case it has frequently a flat surface facing the protoplasm. The structure of the nucleus may vary, being now more leptochromatic, now more pachychromatic. The protoplasm is sometimes quite narrow, but is usually rather abundant and contains coarse granules which generally stain red, exceptionally black purple in Leishman's staining. Sometimes cells containing very few, but in return enormously large granules are met with. By Schulze's synthesis of indophenol-blue most of the granules are not stained—only a few cells contain blue-stained grains. A quite similar result is obtained by Graham's *α*-naphthol-pyronin reaction.

The large mononuclears and poikilonuclears.—This group comprises the cells which I have previously designated as "transition-cells." As this term may give rise to misunderstanding, and as it is no more used in human pathology, I have considered it best to look for other words to replace it. When I now use the designation "large mononuclear cells" I do so quite provisionally and not in order to suggest any relationship to the large mononuclear cells which are met with in normal blood, and which with Pappenheim I call monocytes. The cells in question are partly cells with a round nucleus and narrow protoplasm, partly, and most frequently, cells with irregularly shaped, curved or lobed nucleus and comparatively abundant proto-

plasm. The nucleus is pale, the network of nucleus fine and dense (leptochromatic). The protoplasm contains no grains, and is more or less basophileous. By "poikilonuclear cells" I understand cells which differ from the large mononuclears by the nucleus being completely divided into several pieces (two or three), which are connected by exceedingly fine threads. Hence the question is of some kind of non-granular polynuclears; but because protoplasm as well as nucleus differ from the normal polynuclears I have preferred to give them an entirely new name. When I include large mononuclears and poikilonuclears under one group, it is because they so evidently belong to the same class, so that the restriction of the nucleus, which is so characteristic of the large mononuclears, reaches its highest development in the poikilonuclears. Large mononuclears and poikilonuclears are the predominant kinds of cells in myeloic leucemia, in which they constitute 60 to 70 per cent. of the leucocytes, and through their peculiar form of nucleus contribute to the character of the picture.

The previous group "lymphocytes," which was quite morphologically bounded and comprised both typical lymphocytes and larger forms with a narrow very basophileous protoplasm, I have divided into two, viz., (1) *typical lymphocytes*, identical with normal small lymphocytes, and (2) *lymphoidocytes*. These are morphologically lymphoid cells, but in reality they are not of lymphatic nature, and for one thing differ from the real lymphatic cells by their pronounced protoplasm basophily. In myeloic leucemia, lymphoidocytes are only met with in smaller number; but, as we shall see later on, there are cases in which the number becomes very considerable.

When the leucemia has broken out, the course is of short duration, and the animal dies in the course of 8 to 10 days. On post-mortem examination an enlargement of liver and spleen is revealed, and greyish-red colouring of the bone-marrow in the long bones. The liver is about



TEXT-FIG. 4.—SECTION OF KIDNEY IN MYELOIC LEUCOSIS.

Between the renal tubules a considerable interstitial infiltration of myelocytes is seen.

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twice its normal size, colour reddish ; spleen enlarged 2 to 4 times the normal size.

The microscopical examination shows partly extravascular, partly intravascular changes. Extravascularly one finds accumulations of new-formed myelocytes, most in the liver, less in the kidneys, and only rarely in the spleen. The infiltration in the *liver* forms great roundish accumulations of cells, originating in the periportal connective tissue (200 to 300 μ in diameter). They chiefly consist of typical myelocytes ; yet non-granular cells in a smaller number are not seldom met with between the myelocytes. The myelocytes are not, as in man, imbedded in a reticular stroma, but are placed close to each other, and a stroma is not seen. In this they differ from the lymphatic infiltrates, in which the cells are distinctly separated by a reticular stroma. In certain cases another kind of cells occurs together with the myelocytes, viz., "little dark cells," which to a certain extent are suggestive of small lymphocytes, but must probably be regarded as degenerated myelocytes, which are on the point of dying and disappearing. The periportal infiltrates are rather closely set, and on slight magnification are seen to fill up an area of about the same size as that of the liver tissue itself.

In the *kidneys* reticular, interstitial myelocyte infiltrations are formed in the cortical substance (Text-figure 4). The alteration is frequently dispersed in spots and on the whole not strongly pronounced, in particular it cannot by any means in size be compared with the lymphatic infiltrations. In the *spleen* in which no myeloic tissue is normally found, extravascular myelocyte infiltrations are only exceptionally formed. Finally, as regards the myeloic tissue in the *bone-marrow,* this is generally a little less abundant than normally (concerning this apparently paradoxical phenomenon, see p. 94). Certainly the trabeculæ are in places of normal thickness and full of myelocytes, but in several places they are atrophical and poor in myelocytes. This atrophy surely depends on the heaping up of lymphoid cells in the sinus (" leucostasis ").

In the case of the liver, we find no difficulty in explaining the genesis of the myeloic hyperplasia. For here, even in normal conditions, small accumulations of myelocytes will be found in the periportal connective tissue, which in various pathological conditions increase in size. It is, however, only in leucosis that they reach the extensive development described. As to the kidney the question of the genesis is difficult to answer, as myeloical tissue is apparently lacking in normal conditions. The origin from pre-existing tissue is, however, very likely here too, as on minute examination a very inconsiderable number of myelocytes may be detected in the cortical substance. These conditions: the constant and easily provable presence of myeloic tissue in the liver, the very inconsiderable number in the kidney and the lack of myeloic tissue in the spleen, agree very well with the quantitative conditions of the hyperplasia in leucosis. Thus in the myeloic leucosis there is a general hyperplasia of myeloic tissue in the organs, while the lymphatic tissue is passive or atrophies. In man, as it is known, in different conditions, but most markedly in myeloic leucemia, we meet with a myeloic transformation of the organs (liver, kidney, spleen, lymphatic glands). On account of the difficulty of detecting small myeloic parts of tissue in man, it has so far been impossible to decide with certainty, whether the myeloic transformation originated in tissues present beforehand or in cells, which were derived from the bone-marrow. It is usually assumed that they arise autochthonically, particularly because they are to be found in places in which there is found myeloic tissue in the fœtal state; but the question is, as before mentioned, still being discussed, and the conditions found in the leucosis of fowls must be said to lend a certain support to the theory.

The intravascular changes are the leucostasis in liver, spleen, kidneys and bone-marrow. The whole capillary network in the liver is found dilated and full of large lymphoid cells and myelocytes.

In the pulp of the spleen the same cells are found—particularly the myelocytes are here very numerous. In the kidneys the capillaries may in places be found to be largely filled with lymphoid cells. In addition to the cases which I have described, Schmeisser has in 1915 communicated a case belonging to this group. The case is one of spontaneous leucosis in a fowl, which by the writer is indicated as myeloic, and which is also indubitably of myeloic type, inasmuch as 50 per cent. of myelocytes were demonstrated in the blood, while there were great myeloic infiltrations in the organs.

In a new experimental strain (strain H) I have had the following 2 cases, which I shall briefly describe, as the number of published cases is rather inconsiderable at present.

CASE I

Hen N.S. 335.—March 13, 1919.—I cm^3. emulsion 332 is intravenously inoculated. Hb. 60.

March 28, 1919.—Hb. 20.

April 20, 1919.—Again normal colour.

May 2, 1919.—Hb. 35. Some erythroblasts and a few lymphoidocytes.

May 14, 1919.—Dead. Weight, 950 grms.

Autopsy.—*Liver* large, yellowish ; weight, 110 grms.

Spleen enlarged ; weight, 4·5 grms. ; colour natural. No design on cut surface.

Kidneys brownish, without spots ; size normal.

Bone-marrow soft, jelly-like, red.

Stomach, *intestines*, *thymus*, *skin* and *bones* normal.

Microscopic Examination.—*Liver.*—Very large and close set myelocytic infiltrations (200 to 300 μ) predominate. They consist almost entirely of myelocytes, which are now and then in mitosis. There are only few non-granular cells among them. The lack of granulation apart, these very much resemble the myelocytes. In the capillaries, which are not very much dilated, are mainly seen leucocytes (myelocytes, poikilonuclears, large lymphoid cells), while there are only few erythrocytes.

Spleen.—The follicles small and dispersed. In the pulp tissue there is a very strong infiltration with myelocytes, which often form large accumulations as in the liver. Further non-granular cells, partly poikilonuclears, partly lymphoid, and erythrocytes.

Bone-marrow.—No fat tissue. The trabeculæ of normal thick-

ness, chiefly contain myelocytes, in a few places non-granular mononuclears and poikilonuclears. In the sinuses are seen erythrocytes, myelocytes, poikilonuclears and large lymphoid cells.

Kidney.—There is an extensive infiltration with myelocytes in the interstitial tissue. The vessels filled with blood (myelocytes, poikilonuclears).

As will be seen, the case corresponds very well with the above given description, as a well-pronounced interstitial myelosis is found in liver, spleen and kidney. The blood was unfortunately not examined during life; but in cut preparations leucemia was plainly indicated, the vessels everywhere containing leucemic blood with typical forms of cells (myelocytes, poikilonuclears a.s.o.).

CASE II

Hen N.S. 253.—October 25, 1917.—Intravenously inoculated with 1 cm³. blood emulsion 232. Hb. 35.

November 7, 1917.—Hb. 20. Blood preparation: some normoblasts and megaloblasts. Leucocytes normal.

December 31, 1917.—Hb. 40. Blood preparation on the whole shows normal conditions, a few typical myelocytes are, however, found.

January 17, 1918.—Hb. 35. Erythrocytes normal, leucocytes not augmented, but many myelocytes.

Erythrocytes . . .	1,250,000
Leucocytes . . .	20,000
Differential count of leucocytes :	
Polynuclears . . .	20 per cent.
Myelocytes . . .	25 ,,
Mast-cells . . .	2 ,,
Lymphocytes . . .	48 ,,
Monocytes . . .	5 ,,
	100 ,,

January 2, 1918.—The animal dying; killed. Weight, 510 grms.

Autopsy.—*Liver* of normal size and colour; weight, 20 grms.

Spleen small, yellowish-pale; weight, 0·5 grms.

Kidneys pale yellow, size normal.

Bone-marrow grey-yellowish, a little soft.

Heart, lungs, thymus, skin, bones, intestines normal.

Microscopic Examination.—*Liver.*—Liver cells normal, no

dilation of capillaries. These contain erythrocytes. No peri-portal accumulations of cells.

Spleen.—The follicles slightly pronounced. The pulp tissue without infiltration of cells. The connective tissue in places a little augmented.

Bone-marrow.—The fat-cells have entirely vanished. Trabeculæ very prominent, full of typical granulated myelocytes. Mitoses are frequently met with in these cells. Sinus now and then of normal width, more often, however, narrower than normal. They contain erythroblasts, erythrocytes and a lot of myelocytes.

Kidney.—No pathological changes.

This case is peculiar in several respects. At a certain moment an anemia is found. This, however, disappears later on, and before death only a considerable number of myelocytes is demonstrated in the blood, but no leucemia or anemia. The histologic examination showed, as regards the bone-marrow, a hyperplasia of myeloic tissue, while the other organs presented quite normal conditions. It must, therefore, be regarded as a case of subleucemic myelosis located exclusively in the bone-marrow. The injection of emulsion of the organs produced a typical leucosis in one of the animals treated (N.S. 271).

The aleucemic cases are, as far as can be judged, rare, and are remarkable by the tumour-like form which the hyperplasia assumes. I have previously described a case like this, in which numerous yellowish nodules of the size of a pea were to be found all over the body. They were found in liver, spleen, kidney, heart, thymus and the serous membranes. Microscopic examination of the blood further showed a diffuse myelosis of the organs as in the usual cases. The blood was quite aleucemic.

A case which reminds one very much of this is communicated by Pentimalli. There were nodules in liver, kidneys, ovary, lungs and bone-marrow. They were composed of myelocytes, which everywhere showed numerous mitotic figures. A microscopic examination of the blood was not undertaken during life, no more than in my case ; but microscopy of the organs showed entirely aleucemic blood in the vessels.

Finally, I shall mention that cases occur which show a *combination of myeloic tumours with the above-described typical myeloic leucemia.* I have described such a case.

A hen was suffering from spontaneous leucosis. By post-mortem examination an enlargement of the liver was found, and to a smaller degree of the spleen; enlargement of thymus; colour of bone-marrow pale red; further, some round periostal nodules were found on the interior side of the pelvis, of the size of the kernel of a nut. Microscopy showed the ordinary picture: myelosis and leucostasis in the organs, leucemic blood and plenty of myelocytes in the vessels. The periostal tumours proved to consist entirely of myelocytes. It is easy to see that this case is highly suggestive of the so-called "chloroms" in man. I emphasized this by instituting a comparison with a case of "chlorom" which chanced to arrive for autopsy in Bispebjerg Hospital at the same time.

In addition to these cases, which are closely allied to those formerly described, I have furthermore in strain H had a series of myeloic cases (altogether 8) which presented a somewhat different type. In five of these cases I had the good fortune to get such well-preserved material that it could be used for histologic studies. The object of these was in the first place to find out something about the genesis of some of the dubious forms of cells, viz. (1) the large mononuclears and poikilonuclears; (2) the large lymphoid cells, the "lymphoidocytes."

As an example I shall report the following case:

CASE III

Hen N.S. 196.—June 26, 1917.—1 cm³. blood emulsion 176 is injected intravenously. Hb. 50.

October 30, 1917.—Hb. 20. Blood preparation: some erythroblasts, few myelocytes.

December 12, 1917.—Hb. 32.

December 22, 1917.—Hb. 45.

December 31, 1917.—Hb. 50.

February 14, 1918.—Hb. 40. Blood very viscous.

Erythrocytes . . .	1,640,000
Leucocytes . . .	610,000

Blood preparation shows a pronounced leucemia (Plate II. Fig. 2). The predominant cell form is non-granulated cells with slightly basophilous protoplasm and rather pale nucleus. The latter is roundish, oblong, curved or completely segmented. In the latter case we have cells which might be called polynuclears, but which differ from normal polynuclears by the coarser form of the nucleus. In order to distinguish these from the normal polynuclears, as mentioned before, I use the term "poikilonuclears." By differential count this group of cells constitutes 100 per cent. of the leucocytes; but furthermore a quite small number of myelocytes, polynuclears and lymphocytes are to be found. Only very few erythroblasts and lymphoidocytes (cells with narrow, strongly basophilous protoplasm and circular rather dark nucleus) are met with.

February 19, 1918.—Dead. Weight, 1030 grms.

Autopsy.—*Liver* enlarged; weight, 160 grms.; colour, red-brown without spots.

Spleen very large; weight, 17 grms.; colour, purple. On the cut surface very fine white spots.

Bone-marrow dark red, consistence solid.

Kidneys rather large; weight of right kidney, 11 grms.; colour, brownish.

Lungs, *heart*, *thymus*, *intestines* and *skin* normal. *Bones* normal.

Microscopic Examination.—*Liver*.—Dispersed in the tissue some scarcely medium-sized periportal accumulations of cells, consisting of non-granular cells with oval or curved, sometimes quite lobed nuclei. Among the non-granular cells are seen a very few typical myelocytes. In the capillaries there is blood rich in leucocytes. The leucocytes are of a type similar to that in the dry preparations of the blood.

Spleen.—The follicles atrophic. The tissue of pulp is infiltrated with large non-granulated cells of the same kind as those in the liver infiltrations. The macroscopically visible white spots prove to be due to little roundish masses of connective tissue of about the size of normal follicles and frequently situated round a fine vessel. In the connective tissue here and there hyaline parts.

Bone-marrow.—Fat cells are not seen. The trabeculæ of normal thickness. They contain chiefly non-granular cells, fairly rich in protoplasm, with an irregularly-formed nucleus of the same type as those in liver and spleen, whereas but few typical myelocytes are found. The blood-spaces of normal width and chiefly containing erythrocytes, further, in places, some poikilonuclear leucocytes. In other places erythroblasts are seen. Mitoses are here seen in cells containing hemoglobin.

The remaining 7 cases showed a quite similar picture, for which reason I infer that they all represent a certain type. That which characterizes them is that a single kind of cells, viz., the large mononuclears and poikilonuclears, completely dominates the picture as well in the blood, which is very leucemic, as in the tissues. Here consequently we have the best possible chance of coming to a clear understanding of the nature of those cells.

In the blood preparations (Plate II. Fig. 2) these cells appear partly with a round, but more often with a more or less curved or lobed nucleus. From these lobed nuclei all stages of transition to an entire segmentation are found, so that the single segments of the nuclei are only connected by extremely fine threads in the same manner as in the normal polynuclears. The nucleus is comparatively pale, with rather dense chromatine net. Nucleoli are often seen. The protoplasm may be rather narrow, especially in cells which have a quite round nucleus ; but more frequently it is fairly abundant, almost as in the myelocytes. As a rule it is not granulated, but in certain cases it contains small groups of granules, so that we have transition pictures to the partially granulated myelocytes. The protoplasm is of slightly spongy structure, and is coloured light blue. Thus there is no marked basophilia as in the lymphoidocytes. By oxydase reaction (Graham) they contain no granula.

Now these cells, which are easily recognizable by the peculiar forms of the nuclei and the rather abundant protoplasm, are found, too, in the various organs. In the *bone-marrow* they are to be found in the trabeculæ, as a rule together with some few typical myelocytes. The trabeculæ of the bone-marrow showed a very pronounced hyperplasia in two of these cases, so that the sinuses, which are normally of about the same breadth as the trabeculæ (Text-figure 2), here formed scattered, quite narrow splits (Text-figure 5 and Plate II. Fig. 5). In the two other cases the trabeculæ were of normal thickness, but as the fat tissue had completely disappeared, it must be taken for granted that in

TEXT-FIG. 5.—DIAGRAM OF BONE-MARROW IN MYELOIC LEUCOSIS.

The dark areas are the trabeculæ. Fat-cells are lacking. The light areas are the sinuses which are much narrower than normally.

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these cases also a hyperplasia was present. It is of special interest that the sinus contain leucemic blood, but no accumulation of large lymphoid cells like that which is to be found in the formerly described myeloic cases (leucostasis). In the *liver* there were in all cases found periportal accumulations of the same appearance as the trabeculæ of the bone-marrow. They contained chiefly the same non-granulated cells with a round or irregular nucleus as those in the marrow, and as in this there were here and there typical granulated myelocytes to be seen in between the non-granular cells. Very often mitoses were seen. In the *spleen* the follicles were in all cases atrophic, while the pulp was infiltrated with cells similar to those in the blood. In three of the cases a peculiar change was further found, appearing in the accumulation of large connective-tissue-like cells, situated round a fine vessel. Presumably this is a case of a hyperplasia of the Schweigger-Seydel's capillary sheets. The change appears macroscopically as fine, white spots on the cut surface. For the rest it is not peculiar to myeloic leucosis, but is also now and then to be found in intravascular lymphoid leucosis.

The specific cells in these cases are indubitably of a myeloic nature. I infer this on the following grounds :

1. They are found in the trabeculæ of the bone-marrow of which they are the most essential component, and the hyperplasia of which they cause. Further, they are found as periportal accumulations of cells in the liver, *i.e.* in a place in which also in normal conditions myeloic tissue is present.

2. They are in both of these two cases mixed with sparse, typical myelocytes.

3. In shape, size and structure of the nucleus they much resemble myelocytes, and, like these, are placed very close to each other, in contradistinction to the lymphocytes in the lymphatic leucosis, which are embedded in a distinct reticulum.

4. In some cases (in the blood preparations) they may

possess a slight partial granulation, by which transition pictures to the typical myelocytes are formed.

5. They constantly show a development of the nucleus in the direction of a strong segmentation, by which the so-called " poikilonuclear " cells arise.

According to the terminology in general use the cells here in question may be named *myeloblasts, i.e.* non-granular myelocyte forms, irrespectively of the fact that such cannot be regarded as normal pre-phases of myelocytes in fowls. Thus the term is not quite correct ; but as similar objections may be raised to the use of the word in human pathology, I have no hesitation in using it about the cells in question, which are only non-granular myelocytes.

Hence, under the influence of the virus of leucosis, in some animals we meet with a hyperplasia of myeloic tissue ; but while this in several cases (viz. Cases I. and II. and those formerly communicated) apparently is of normal character, it happens in other cases (Case III.) that the forming of the granules ceases, while a development of the nuclei in the direction of a total segmentation partly remains. While normally we have the series :

Myelocyte→Metamyelocyte→Polynuclear,

in the last-mentioned group of cases of leucosis we get the following series :

Myeloblast→Metamyeloblast→Poikilonuclear.

After this we may be justified in distinguishing between two subdivisions within the myeloic leucosis, viz., the " *myelocyte type* " and the " *myeloblast type.*" In the myelocyte type we meet with some non-granular cells in the myelocyte infiltrations, *e.g.* in the liver, which according to their whole appearance and occurrence must be understood as myeloblasts. On the other hand, in the myeloblast type some few myelocytes are always seen in the myeloblast accumulations, and in one of the cases the number of myelocytes in the bone-marrow was fairly considerable. Hence it is evident that a distinct line cannot be drawn between the two types, but that transition forms are found.

The Poikilonuclear Cells

As said before, these cells remind one to a great extent of the normal polynuclears ; but partly they are completely non-granular, partly the segments of the nuclei are larger, paler, and vary more in size (Plate II. Fig. 2). I have previously, in describing the myeloic leucosis, emphasized that there is no question of an augmentation of the polynuclears as in the myeloic leucemia of man, as the relative number is greatly diminished, and the absolute number at any rate not augmented. In the former count the poikilonuclear cells and the large mononuclears were placed in the group "transition-cells." As it has now become evident that the poikilonuclears must be regarded as pathologic polynuclears, the above observation needs correction to the effect that there is certainly not any augmentation of the normal polynuclears, but that the number of normal and pathologic polynuclears together may be augmented. One of the new cases is an exceedingly eloquent example as to the correctness of regarding the poikilonuclears as pathologic polynuclears. In this case we find, at the first blood examination (October 30, 1917), a large percentage of polynuclears (38 per cent.) corresponding to a considerable absolute augmentation of these cells (123,500 per mm^3.) ; but it must be remarked that they are pathological cells, in a stage half-way between the normal polynuclears and the poikilonuclears, the rod-shaped granules being few and quite small, while the segmentation of the nuclei is atypical. Thus we have here an enormous augmentation of the polynuclears ; the picture is evidently on its way to the non-granulated type, and by the second examination (November 10, 1917) the change has occurred. Now only few real polynuclears are seen, whereas cells of the myeloblast series predominate. As known, the myeloblast type is not rare in the myeloic leucemia of man. Also the change from the granular type to myeloblast leucemia is often noticed in man, especially in the last stages of the disease. In the myelocyte leucemia of man the myeloblasts have generally

an undivided round nucleus ; but cases are also known, in which the nuclei have developed a strong segmentation, so that non-granular polynuclears are formed (Pappenheim's "leucoblastische Riederzellen"), corresponding to my poikilonuclears. Pappenheim has described similar cells in sarcoma in mice.

The Lymphoidocytes

As previously mentioned, by this I understand non-granular cells with a homogeneous, dark, circular nucleus and narrow, very basophilous protoplasm. These cells are characteristic of the intravascular leucosis (Plate III. Figs. 3 and 4), but are also frequently met with in smaller number in the myelocyte type of myeloic leucosis. I have previously fancied that they might be myeloblasts. As it has appeared, however, that they are somewhat different from the above-described real and undoubted myeloblasts (Plate II. Fig. 4), and as they are not, or only quite exceptionally, found in the blood in the pronounced and pure cases of myeloblast leucosis, as also leucostasis in the organs here is lacking, there are good grounds for regarding them as a special kind of cells, peculiar to the intravascular leucosis and unconnected with myelosis. When, nevertheless, they appear in the myeloic leucosis, it must be regarded as a combination of two different processes.

As an example of such a combination I may quote the following case :

CASE IV

Hen N.S. 320.—January 8, 1919.—1 cm^3. Blood emulsion 296 is inoculated intravenously. Hb. 52.

February 18, 1919.—Hb. 25. Marked leucemia.

February 20, 1919.—Hb. 20. Blood preparation unchanged. The predominant kind of cells is a large mononuclear leucocyte with non-granular protoplasm and irregularly shaped nucleus. Some poikilonuclears. Rather few myelocytes. The polynuclears of normal aspect. Of lymphocytes, chiefly the small forms. The erythrocytes on the whole of natural aspect ; only few erythroblasts. Some "lymphoidocytes" with homogeneous dark nucleus

and quite narrow, very basophilous protoplasm. Very few mitoses.

Erythrocytes . . .	1,066,000
Leucocytes . . .	267,000

Differential count of leucocytes :

	Per Cent.	Absolute Numbers.
Polynuclears	1	2,670
Myelocytes	4	10,680
Myeloblasts and Poikilonuclears . .	63	168,210
Lymphocytes	1	2,670
Lymphoidocytes	31	82,770

Dead at 2 o'clock. Autopsy at 3½. Weight, 1200 grms.

Autopsy.—*Liver* very large ; weight, 154 grms. Colour uniformly red, with sparse fine white spots.

Spleen enlarged ; weight, 12 grms. ; colour, purple. No design on cut surface.

Bone-marrow firm ; colour, reddish.

Kidneys enlarged ; weight of right kidney, 13 grms. Surface a little rough, with traces of spots.

Stomach, *intestines*, *thymus*, *skin* and *bones* normal.

Microscopy.—*Liver.*—Some medium-sized periportal cell infiltrations are found, consisting partly of myelocytes, partly of myeloblasts. The capillaries are very much dilated and filled with regular round " lymphoid " cells with a circular nucleus and narrow protoplasm. Besides, rather sparse poikilonuclear cells and erythrocytes are found.

Spleen.—Follicles sparse and small. Pulp tissue much infiltrated with large, round " lymphoid " cells like those in the capillaries of the liver. Here and there small groups of myelocytes.

Bone-marrow.—Fat-cells are seen here and there, but their number is much decreased. The trabeculæ are partly of normal thickness and contain myelocytes or more frequently myeloblasts and poikilonuclear cells ; in other places they are narrow and contain small dark cells, or they are quite atrophic. In the trabeculæ, which are well developed, mitoses are met with in the myeloblasts. Sinus is partly dilated, corresponding to the atrophic trabeculæ. They contain great masses of regularly shaped lymphoid cells, mixed with sparse erythrocytes and poikilonuclears.

Kidneys.—Scarce stripe-shaped interstitial infiltration of myelocytes and poikilonuclears. The capillaries excessively filled with large " lymphoid " cells and sparse erythrocytes.

In this case we have a leucemia of the myeloblast type, as there is a great number of cells in the blood (168,210 per

mm³.) belonging to the myeloblast series ; but, further, the blood preparation shows a considerable number of lymphoidocytes (82,770 per mm³.), which in well-stained preparations are distinguishable without difficulty from the myeloblasts. The histological examination is seen to agree very well with the blood picture, as on the one side we find deposits of myeloblasts in the liver and to a smaller degree in the bone-marrow, while on the other is seen a well-marked " leucostasis " in the liver and the capillaries of the kidneys, as well as in part of the sinus of the bone-marrow, in the latter accompanied by atrophy of the trabeculæ.

Thus the result is that the lymphoidocytes, which are found accumulated in the capillaries, and circulating in the blood, in some cases of myeloic leucosis, do not necessarily pertain to the type. These cells are not mycloic cells, but they are identical with the cells which are met with in the intravascular, lymphoid leucosis. Their nature and origin will further be dealt with in the chapter on this form of leucosis.

Above I have touched upon various analogies between myeloic leucemia in man and the myeloic leucosis of fowls, more particularly the occurrence of a myelocyte and a myeloblast type ; the change in the course of the disease from one blood picture showing granular cells to another showing cells of the myeloblast series ; the occurrence of cases combined with development of tumours ; finally the aleucemic cases. As objections have been raised in various quarters to the advisability of regarding the leucosis of fowls as a disease of the same kind as the leucosis of man, and to the right to establish analogies, I will finally quite briefly make mention of a single phenomenon, viz., the leucemical change in the blood. This change, which is characterized by the extraordinary augmentation of the number of leucocytes, and the occurrence of unripe forms, is the classical symptom which is not seen in other diseases. Conditions which somewhat remind one of leucemia are partly hyperleucocytosis in which an augmentation of the number of leucocytes occurs, but

without the occurrence of pathological forms, partly the so-called leucemoid blood pictures, which are due either to various infectious diseases or to tumours located in the bone-marrow. Hyperleucocytosis is known also in fowls in various infectious diseases, and has been described, *e.g.*, in tuberculosis by Hirschfeld & Jacoby and by Ellermann & Bang, but it presents a picture which cannot be mistaken for the real leucemia. Leucemoid conditions may no doubt be met with, and have, for instance, been described by Pappenheim in experiments with blood poisons. As in man and other mammals, apart from the fact that changes in the blood and organs do not reach the same degrees as the real leucemia, a palpable cause of the disease (tumours, bacterial infections) will always be found. For this reason no parallel can be drawn between the leucemoid conditions in man and leucemia in fowls. It is just as great a mistake, when, for instance, Folke Henschen wants to make the leucosis of fowls analogous to the well-known disease of infants, anemia pseudo-leucemica infantum. This author quotes a single case in support of this, in which he diagnosed an anemia, complicated with myelosis, in the organs of a hen. The analogy is a failure, because anemia in infants as a rule is a benign disease in contradistinction to leucosis, which both in man and in fowls nearly always is fatal. Further, infantile anemia, as the name implies, lacks just this leucemical change in the blood.

Already from the previous works it appears that certain cases of leucosis in fowls show a pronounced leucemia. Still it is perhaps not unnecessary once more to emphasize the reality of the blood change on the ground of the new material which I have had in strain H. In the following table (Table VI.) all the cases are specified.

The number of leucocytes is given wherever it has been counted. Where no such count was made only "leucemia" is put down, *i.e.* a blood change of the same degree and character as in counted cases. It will now be seen that, while the number of leucocytes normally is

about 30,000, numbers between 200,000 and 600,000 are here met with. In a single case even a number of 2 millions was demonstrated. Thus, it is a question of a considerable augmentation, and of numbers similar to

Table VI

Value of Hemoglobin and Number of Leucocytes in a Series of Leucemic Cases

	Hemometer Number.	Hemoglobin Percentage.	Leucocyte Number.
		Corr.	
N.S. 196 . .	40	67	610,000.
N.S. 205 . .	20	33	325,000.
N.S. 233 . .	28	47	Ca. 2 mill.
N.S. 236 . .	38	63	Leucemia.
,, . .	25	42	495,000.
N.S. 300 . .	25	42	Leucemia.
N.S. 320 . .	25	42	,,
,, . .	20	33	267,000.
N.S. 326 . .	30	50	Leucemia.
N.S. 332 . .	20	33	271,000.

those of myeloic leucemia in man. As regards the hemoglobin numbers, it is necessary, for being able to compare these with those of man, to multiply them by 100 : 60, as the zipher 60 (Sahli) corresponds to 100 in man. Now in 2 cases a hemoglobin number of 60 to 70 per cent. is found, and in no case a lower value than 30 per cent. A marked leucemia might thus be present without any particular anemia. In comparison with this it may be mentioned that the hemoglobin number in intravascular lymphoid leucosis and in pure anemia rarely transcends 30 per cent., and frequently descends to 10 to 15 per cent.

Thus the myeloic leucemia of fowls can be understood neither as anemia, as hyperleucocytosis nor as a leucemoid state; but, according to the commonly recognized definition, it must be regarded as a pure leucemia.

VIII

THE INTRAVASCULAR LYMPHOID LEUCOSIS

THE intravascular lymphoid leucosis [1] is a very curious type of disease, which it is not possible to rubricate at once, as the anatomical findings are peculiar and the histogenesis for the present quite obscure.

After a period of incubation the disease begins with anemical symptoms. The animal is less lively than usual, the colour of the comb is yellowish-pale and the hemoglobin number proves to be reduced to 20 to 25 (Sahli). Counting the erythrocytes the number proves to be reduced to about a million, consequently to a third of the normal. On examination of dry preparations of the blood (Plate III. Fig. 3), polychrome erythrocytes are found in considerable numbers. The leucocytes are generally not augmented and the cell forms are the normal ones. Generally, however, pathological cells are also to be found, viz., myelocytes and lymphoidocytes. The myelocytes are very scarce in number, and usually it is not possible to find more than a few specimens in each preparation. The lymphoidocytes, on the other hand, are more frequent. The following composition may, for instance, be found :

Polynuclears	13	per cent.
Mast-cells	0·5	,,
Monocytes	1·5	,,
Lymphocytes	15	,,
Lymphoidocytes	70	,,
	100	,,

[1] The name is merely tentative. I use the term "lymphoid" quite morphologically for cells which resemble the lymphocytes, while for the undoubted lymphocytes I use the term "lymphatic."

As will be seen, there is a great preponderance of lymphoidocytes; but the percentage number may rise still higher (to 90 per cent. or more). Sometimes the absolute number may also be increased. This being the case the picture may be characterized as subleucemic or leucemic. The anemia usually lasts till death, but in several cases pronounced variations in the degree of the anemia is seen, and complete remissions of shorter or longer duration are not rare. In certain cases the improvement of the disease is apparently permanent, in so much as the hemoglobin number is normal, but all the same death occurs, and the anatomical findings do not differ from the ordinary cases, in which the anemia is continued.

On autopsy is found an enlargement of liver and spleen (Text-figure 6) and a greyish-red colouring of the bone-marrow. The liver may be enlarged up to four times its normal (in weight). The colour is reddish and quite uniform without white spots. The spleen is enlarged to a similar degree. The proportions, however, are very variable, as I shall subsequently show.

The microscopical picture is marked by the "leucostasis." By this I understand an accumulation of lymphoid cells in the vessels in various organs, especially in liver, spleen, kidneys and bone-marrow. In the *liver* the alteration is usually quite evenly dispersed throughout the whole organ. The capillaries are everywhere seen to be dilated and full of lymphoid cells, between which there are scarce erythrocytes (Plate III. Fig. 1). While the capillaries in the organs taken out are normally fallen in or, if filled with blood, are of the breadth of from one-third to one-half of that of the trabeculæ of the liver cells, in the leucostasis they have a diameter, which is just as large as that of the trabeculæ of the liver-cells, and at times a still greater diameter (2 to 3 times as large). The cell-filled capillaries form a connected network, which owing to its darker colour forms a contrast to the pale trabeculæ of the liver-cells. The picture is frequently so regular that on slight magnification it resembles an

Text-fig. 6.—Enlargement of Liver and Spleen with Intravascular Lymphoid Leucosis.

To the right the leucemic organs, to the left normal organs. Three-fourths of natural size.

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injection with dark-coloured injection material. One has the impression of dealing with a motionless mass of cells and not with circulating blood, an impression which is strengthened by the detection of numerous mitoses in the lymphoid cells. This leucostasis, which is the cause of the very often considerable enlargement of the organ, is in itself a strange phenomenon. How is it possible that in the vessels themselves, within a limited domain, there can be accumulated great masses of cells, while the circulating blood only contains a few of the cells in question? That this is really the case cannot be doubted. Any thought of it being an agonal or post-mortal phenomenon must at once be rejected. How the leucostasis arises must for the present remain doubtful. For comparison I shall only recall the accumulation of leucocytes in inflammation, and the intravascular occurrence of erythroblasts in the vessels of the bone-marrow; there is, however, no resemblance to an ordinary blood stasis or a thrombosis.

A quite similar leucostasis is to be found in the *kidneys* (Text-figure 7). Here, however, the process is not equally dispersed throughout the organ, but is limited to smaller, scattered domains. In the *spleen* is found an equally dispersed infiltration with lymphoidocytes of the pulp tissue, while the follicles are small or quite atrophied. In the *bone-marrow* the leucostasis is generally very much pronounced, and the special condition that the tissue is surrounded by a firm bone capsule involves the destruction of the trabeculæ of the bone-marrow by the mechanical effect of the leucostasis.

As the final stage, hence, is seen a mass of cells in which, on minute examination, will be discovered narrow strings poor in cells and something like connective tissue, which are atrophied remains of the trabeculæ (Text-figure 8 and Plate III. Fig. 2). The normal spongy tissue, in which solid tissue and vessels are almost equally developed, has thus by the atrophy of the trabeculæ been transformed into a kind of cavernous tissue. It is not unlikely that

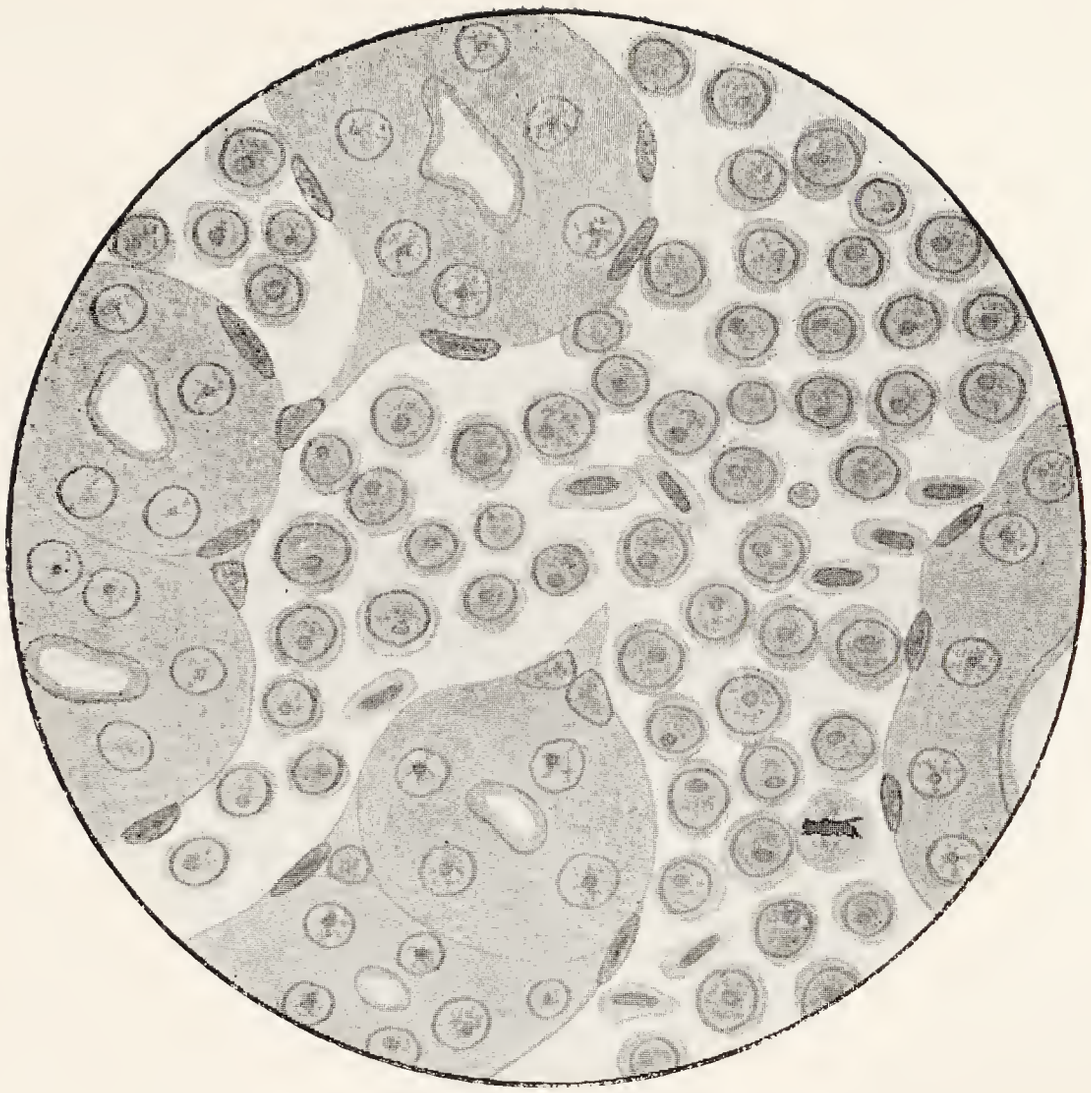
the atrophy of the follicles of the spleen arises in a similar way.

Thus the leucostasis is the predominant element, and that which conditions both the enlargement of the organs and the atrophy of certain tissues. At times, however, one also finds another process, viz., a myeloic hyperplasia of the liver. Scattered periportal accumulations of myelocytes may be found; they are most frequently small or medium-sized, and never developed as much as in the myeloic leucosis. The alteration must be understood as a finding of secondary importance, and is entirely lacking in some cases. Later on I shall come back to the explanation of this alteration.

In my treatise *Die übertragbare Hühnerleukose*, I have left unanswered the question of the nature of the lymphoid intravascular leucosis, as I did not venture to decide whether it was a lymphatic or a myeloblastic or a primordial-cell leucemia, or if the cases were possibly different.

In my experiments with the experimental strain H, I have had good opportunity of studying this type, as I had altogether 18 cases at my disposal. In the first place, it proved that these cases, which were derived from a spontaneous case of mixed character (myeloic leucemia with many lymphoidocytes), and which occurred in conjunction with some myeloic cases, were in every particular absolutely identical with the intravascular lymphoid cases in strain E, which were derived from a spontaneous lymphatic case, and besides showed predominant lymphatic character. Further, it became more and more evident that it was a quite definite well-defined type of disease, which probably always had the same genesis.

On reviewing the possibilities, which might beforehand be taken into consideration, the possibility that the cases might be of a lymphatic nature may surely be entirely disregarded. The fact is that not the slightest trace of a lymphatic hyperplasia is to be found in the organs. On the contrary, the rule is that the lymphatic follicles in the



TEXT-FIG. 7.—LEUCOSTASIS OF THE KIDNEY.
Capillaries dilated and filled with lymphoidocytes and erythrocytes.

TEXT-FIG. 8.—LEUCOSTASIS OF BONE-MARROW, WITH ATROPHY OF THE TRABECULÆ.

The dark areas are trabeculæ. The light ones the dilated sinuses which are filled with lymphoid cells.

spleen are more or less atrophied, so that they have often entirely disappeared. Similarly hyperplasia of the small accumulations of lymphocytes in the liver or in any other places is never seen. In contradistinction to the lymphatic leucosis the changes are quite intravascular. Also the individual cells are different in the two types of disease.

If, next, we consider the possibility that it might be a myeloic leucosis, the question might previously be rather dubious, since in this disease a leucostasis in the organs and lymphoidocytes in the blood were also demonstrated. Later experiments, however (look above), showed that leucostasis in the blood is no constant concomitant of the myeloic leucosis, as the leucostasis is lacking in the pure cases, or, when present, must be understood as a phenomenon not connected with the myelosis itself. Absolutely antagonistic to the notion of the myeloic nature of the disease is the fact that the proliferation in the bone-marrow originates in the venous sinus, while the myeloic tissue atrophies and may finally entirely disappear. Nor will a hyperplasia of myeloic tissue necessarily be found elsewhere.

It may therefore be taken for granted that intravascular lymphoid leucosis is neither myeloic nor lymphatic, but also as regards the genesis is an independent form, *i.e.*, a third type of leucosis.

In the previous works I have recorded so many cases of leucosis belonging to this type that it is unnecessary here to go into details as regards the individual cases of the new strain, so I shall instance only a single case :

CASE I

Hen N.S. 204.—June 22, 1917.—1 cm³. of blood emulsion 171 is intravenously injected.

September 18.—The last days pale. Hb. 25. Blood preparation : some polychrome erythrocytes. Some lymphoidocytes. A few myelocytes.

September 30, 1917.—Hb. 15. Numerous polychrome erythrocytes and erythroblasts. Scarce myelocytes and lymphoidocytes. The leucocytes are not augmented.

November 14, 1917.—Hb. 25. Blood preparation unaltered. The animal dying ; killed. Weight, 960 grms.

Autopsy.—*Liver* large ; weight, 80 grms. ; colour, pale brownish-red, without spots.

Spleen very large ; weight, 14·5 grms. ; colour, pale red, no design on cut surface.

Kidneys pale. Weight of right kidney, 6·5 grms.

Bone-marrow greyish-red, rather solid.

Skin, *thymus*, *lungs*, *heart*, *digestive tube* and *bones* normal.

Microscopy.—*Liver.*—Liver cells normal. The whole capillary network is very much dilated and filled with great lymphoid cells. They have a regular, normal nucleus containing one or two great round nucleoli, and a network with some few chromatine grains. The protoplasm is narrow, non-granulated. Scarce erythrocytes and erythroblasts are found among these. In a few places quite small periportal infiltrations consisting of myelocytes are met with.

Spleen.—The follicles are lacking or are only in a few places seen as slight traces. The hyperplastic pulp tissue is very much infiltrated with great lymphoid cells like those in the liver. Here also plenty of mitoses are met with. Further scarce myelocytes, erythrocytes and macrophages, full of the remains of erythrocytes, are found.

Bone-marrow.—The trabeculæ, generally shrunken to quite narrow strings with a few cells of connective tissue but without myelocytes, show a marked atrophy. Cells with well-conserved myelocytes are only very sparsely found. Also the fat-cells have entirely disappeared. The enormously dilated sinus contain chiefly the same lymphoid cells, which were found in liver and spleen. In these numerous mitoses are seen. In some few places larger accumulations of erythrocytes are met with ; they are generally found in small number among the lymphoid cells. Erythroblasts with hemoglobin-poor protoplasm are also seen.

Kidney.—In the capillaries there are frequently considerable accumulations of lymphoid cells mixed with erythrocytes. No interstitial cell infiltrations.

As seen, the case thoroughly corresponds to the type. There is the typical change in the blood ; the enlargement of liver and spleen, a consequence of the leucostasis of the vessels ; atrophy of the trabeculæ of the bone-marrow and leucostasis of the sinuses.

In seven of the remaining cases a considerable enlargement of the organs was found, while these in the rest of the cases were only enlarged to a smaller degree. The micro-

scopical alterations were of the same kind, and in the main identical with those described in Case I. In some cases, but by no means constantly, were found erythrophages or pigment cells in the spleen. In some cases a perivascular accumulation of connective-tissue cells was found round the fine arterial capillaries. This caused a formation of light spots of about the same size as the normal follicles of the spleen.

Special interest attaches to the *conditions of the blood.* Anemia was demonstrated in most of the cases ; in a few cases, however, a remission occurred, so that the hemoglobin number again attained its original height. This, however, did not mean recovery from the disease, as the animal died, and on post-mortem examination showed the ordinary findings. The blood picture was nearly quite the same in all the cases. Peculiar is the occurrence partly of unripe forms of erythrocytes : polychrome erythrocytes and erythroblasts, partly of lymphoidocytes (Plate III. Fig. 3). The lymphoidocytes were in some cases so numerous that one could speak of a subleucemic or leucemic picture. The erythroblasts which can appear in normo- as well as in macro- and microforms have a nucleus that differs from the pycnotic nucleus of the ripe erythrocytes in being larger, paler, more roundish and in having a pronounced chromatin structure, the chromatin forming separate large angular particles. The protoplasm may be of normal hemoglobin content, but more frequently it is paler, yellowish, greyish or more or less blue. In the latter case the nucleus is commonly comparatively large, quite circular, and the protoplasm forms a narrow border. These cells show gradual transitions to lymphocyte-like cells with distinct chromatin structure and from these to typical lymphoidocytes. These are identical with the lymphoid cells which are found accumulated in the capillaries in the various organs, as may easily be ascertained by examining dry preparations from the organs after Leishman staining. Generally the *lymphoidocytes* are rather large cells which measure 8 to 14 μ in diameter. The nucleus is always

circular, while the protoplasm forms a very narrow border round the comparatively large nucleus. Now and then it may be more abundant, and then one gets pictures resembling the so-called " Reizungszellen." The nucleus is stained purple with Leishman staining, and by this shows a nearly homogeneous structure. One or several nucleoli are found, but are, as a rule, covered by the colouring. The protoplasm shows a plain border, but from this small lingulate runners are often seen to extend. The structure is fairly homogeneous, but it often contains more or less clear vacuoles. It is extremely basophilous, taking a deep blue shade with Leishman staining. The colour is much stronger than in the protoplasm of lymphocytes, but generally also stronger than the colour of the myeloblasts. The difference is most conspicuous if both forms of cells happen to occur in the same preparation, and when one has a suitable, not too strong colouring (Plate II. Fig. 4).

By staining in a weak solution of methylen-blue the protoplasm of the lymphoidocytes also stain a strong blue and form a contrast to the nucleus, which apart from the nucleolus is quite unstained. The myeloblasts, on the contrary, on staining in methylen-blue show about the same strength of colouring in nucleus as in protoplasm, so that even the contour of the nucleus may be difficult to distinguish.

As mentioned above, in the blood preparation every imaginable transition, from typical lymphoidocytes to basophilous erythroblasts, and from these to the complete erythrocytes are found. The picture varies very much, however, as one finds partly micro-, normo-, and macroforms of the different phases of development, partly that the development of the nucleus and of the protoplasm do not always go exactly together. However, one sees only the " transition pictures " and not the transition itself. I shall therefore state the other reasons which may be adduced in favour of assuming the lymphoidocytes to be hemoglobin-free pre-phases of the erythrocytes.

1. The lymphoidocytes always accompany the erythro-

blasts in the blood preparations. Likewise in the leucostasis they are constantly found mixed with erythroblasts and erythrocytes in the various organs.

2. The forming of lymphoidocytes in the bone-marrow only takes place in the sinuses, *i.e.*, in the place in which the erythrocytes are normally formed, while the trabeculæ of the bone-marrow are quite passive and atrophy.

3. A small number of lymphoidocytes is normally found in sinuses of the bone-marrow and must be understood as pre-phases of the normal erythroblasts (Denys).

4. Lymphoidocytes are exclusively found intravascularly in the intravascular lymphoid leucosis, as the spaces of the pulp of the spleen must, in this respect, be reckoned to the vascular system. But, on the other hand, they do not, like myelocytes, myeloblasts or lymphoblasts, form extravascular infiltrations.

5. In lymphoidocytes as well as in erythroblasts and erythrocytes, twin-nuclei frequently occur in the intravascular leucosis (Plate III. Fig. 5). We are here dealing with a phenomenon which, according to my experience, is not known in myelocytes or myeloblasts, any more than in the normal or pathologic lymphatic cells. The two nuclei are exactly alike in size as well as in shape. In the erythrocytes they are round or oval, while in the lymphoidocytes, in which they are very large and almost fill out the cell body, they often show a flattening of the sides facing each other (Plate III. Fig. 5*a*, *b*). Twin-nuclei probably arise by a division of the nucleus which is not followed by a division of the cell.[1]

The above shows that *lymphoidocytes are erythrocytic cells in the first stage of development* (*erythrogonies*), *and that the intravascular lymphoid leucosis must for this reason be regarded as an erythroleucosis.*

[1] I have lately had the opportunity of detecting twin-nuclei also in man, viz., in a case of leucemia, in which they appeared in the normally stained as well as in the polychrome erythroblasts. Neither in manuals nor in treatises have I been able to find reports of twin-nuclei in erythroblasts. On the other hand, I have sometimes found pictures of them, but no further mention.

After this it is necessary to examine the relationship between the hitherto described typical intravascular lymphoid leucosis and the entirely anemical forms. By this I understand cases of anemia in which changes in the organs are in the main lacking. In strain H there was a quite even transition between these types so that in certain cases it was a matter of taste what designation one would give the case. If we look at the cases marked "intravascular lymphoid leucosis," in half the cases we find a pronounced swelling of the organs, and corresponding to this microscopically a severe leucostasis. In the other cases the swelling of liver and spleen was only slightly pronounced, and the microscopical changes were slighter. Only in sinus of the bone-marrow the leucostasis was always well pronounced. Of cases standing on the point of transition to pure anemia I shall report the following :

CASE II

Hen N.S. 290.—May 7, 1918.—Hb. 45. 1 cm^3. of blood emulsion 277 is intravenously injected.

August 28, 1918.—For some days a little pale. Hb. 10. Blood preparation shows polychrome erythrocytes, erythroblasts and scarce lymphoidocytes. Dying ; killed.

Autopsy.—*Liver* of normal size ; colour yellowish ; weight, 45 grms. *Spleen* not enlarged ; colour purple. Weight, 3 grms.

Bone-marrow of firm consistence, red, but paler than normal. All other organs normal.

Microscopy.—*Liver.*—The capillaries are not dilated, but contain small groups or small rows of large lymphoid cells. The periportal accumulations of cells are slightly enlarged and contain myelocytes and small dark cells. The larger vessels contain only few cells (erythrocytes and lymphoid cells).

Spleen.—The follicles are distinctly visible everywhere ; they are not, or to a small degree, diminished. They contain small lymphocytes, now and then even normal germinal centres with mitoses. In the pulp tissue plenty of erythrocytes and some large lymphoid cells are seen.

Bone-marrow.—The trabeculæ, partly quite atrophied, partly very much shrunken ; in the latter case they contain myelocytes and small dark cells.

The changes in the liver are here very slight, and the organ is not enlarged. In the spleen there is only very slight accumulation of erythrogonies and the follicles are well developed, so that it is even possible to detect germinal centres. Only in the bone-marrow the leucostasis is pronounced.

In the following table the 4 cases of " pure anemia " are specified (Table VII.).

In these cases, corresponding to those formerly described, we find no enlargement of liver and spleen, and the microscopy, too, shows quite normal conditions : no leucostasis and no periportal cell-infiltrations. In two of the cases the bone-marrow shows atrophy of the trabeculæ. Leucostasis is found in all 4 cases, but is only slightly pronounced in 2 of them. Sinuses are here mostly full of serous fluid. Blood preparations show erythroblasts in all 4 cases, lymphoidocytes (erythrogonies) only in 2 of them.

Hence it seems justifiable to me to include the intra-vascular lymphoid and the anemic leucosis under one form, the erythroleucosis, as in all these cases it is the erythrocytic system which is attacked by the disease. The pure anemia is not a special form, but only the one extreme of a continuous series, at the other end of which is the lymphoid intravascular leucosis with pronounced alterations in the organs. By destruction of erythrocytes, anemia with secondary regeneration arises. This latter, in contradistinction to the simple anemia, which, for instance, is found in the tuberculosis of fowls, has a marked " pernicious " character, as partly there occurs basophilous erythroblasts, partly still more inferior forms, erythrogonies.

In the cases of " pure anemia " the hemoglobin number always seems to be very low (10 per cent.). As, besides, the regeneration phenomena are very slight in comparison with the " lymphoid " cases, these cases may perhaps be understood as a kind of comparatively aplastic anemias. The hemoglobin number in the lymphoid leucosis is frequently rather high, may at times rise to normal value. In

TABLE VII

Synopsis of Four Cases of "Pure Anemia"

No.	Blood.	Liver.	Spleen.	Bone-marrow.
N.S. 197. Weight, 490 grms.	Hb. 10. Numerous erythroblasts. Many lymphoidocytes. Picture subleucemic.	Weight, 17 grms. No cells in the capillaries. Slight periportal infiltrations.	Weight, 1 grm. Follicles small. In the pulp some lymphoidocytes. No erythrophages.	Total atrophy of trabeculæ. In sinus coagulated serous fluid and erythrocytes. Few erythroblasts, no lymphoidocytes.
N.S. 231. Weight, 1000 grms.	Hb. 10. Numerous erythroblasts. Lymphoidocytes very scarce.	Weight, 32 grms. Capillaries empty. No periportal cell infiltrations.	Weight, 1·2 grm. Follicles of normal size. No cell infiltrations in pulp. No erythrophages.	No atrophy of trabeculæ. Sinus crowded with lymphoidocytes.
N.S. 237. Weight, 600 grms.	Hb. 10. Erythrocytes, 650,000. Many erythroblasts and lymphoidocytes (mitoses).	Weight, 23 grms. Capillaries empty. No periportal cell infiltrations.	Weight, 1 grm. Follicles of normal size. Pulp natural. No erythrophages.	Trabeculæ as a rule atrophied. In sinus chiefly coagulated serous fluid and lymphoidocytes.
N.S. 245. Weight, 940 grms.	Hb. 20. Some polychrome erythrocytes and erythroblasts. Very few lymphoidocytes.	Weight, 38 grms. Capillaries empty. No periportal cell infiltrations.	Weight, 1·5 grm. Follicles of normal size. Scarce lymphoidocytes in pulp. No erythrophages.	Trabeculæ in spots atrophied, few myelocytes. Sinus full of lymphoidocytes.

such cases, which according to the above must be understood as compensated anemias, an increased index may at times be demonstrated, and in a single case pronounced chronical gastritis was found.

When formerly discussing the causes of the anemia in the intravascular lymphoid leucosis, I mentioned two possibilities of explanation, one chemical and the other mechanical. The supposition of the effect of a hemolytic toxin most naturally suggested itself, but, besides, I fancied that the proliferation of lymphoid cells would quite mechanically injure the erythrogenesis. This idea is not reconcilable with the understanding now gained of the true nature of the lymphoidocytes. This, however, does not mean that the growing masses of erythrogonies are not able to exercise a mechanical effect. The atrophy of the trabeculæ of the bone-marrow is most easily explained in this way, as an atrophy by pressure. The atrophy of the spleen follicles is evidently due to the same cause.

Previously I have taken it for granted that a destruction of the erythrocytes by a hemolytic toxin was the primary process, while the remaining phenomena were the outcome of an atypical regeneration. This conception corresponds to that usually maintained as regards the pernicious anemia of man. In this disease, however, several investigators (Cohnheim, Ehrlich and recently Nægeli, Ferrata) have attached a primary importance to the alteration in the bone-marrow. Considering the enormous growth of erythrogonies in the erythroleucosis of fowls, one feels tempted to think of such a direct influence, by which would also be gained a certain accordance with the two other types of leucosis in which the proliferation of cells is the essential feature. This assumption, however, lacks every basis of facts, and it is therefore an open question whether the growth of the erythrogonies is produced by the hypothetic toxin of the disease or by products of the disease proceeding from the cells of the organism. It must be supposed that erythrogonies, like leucocytes and other cells, are resistant to hemolytical toxins. The hypothetic hemolysin,

therefore, will electively destroy the hemoglobin-containing cells, while it spares the erythrogonies. Here we have one of the conditions of the development of the leucostasis, but other things may, of course, be involved.

The alteration in the conception of lymphoid intravascular leucosis involves various practical consequences. In the first place, it will no more be possible in the counting (and differential counting) of the leucocytes to class the lymphoidocytes among the leucocytes. If, then, the lymphoidocytes are eliminated from the differential count given at the beginning of this chapter, the result will be as follows :

Original Form

Polynuclears . .	13 per cent.
Mast-cells . . .	0·5 ,,
Monocytes . . .	1·5 ,,
Lymphocytes . .	15 ,,
Lymphoidocytes . .	70 ,,

After Correction

Polynuclears . .	43·3 per cent.
Mast-cells . . .	1·7 ,,
Monocytes . . .	5 ,,
Lymphocytes . .	50 ,,

One will notice that the percentage proportions are in reality quite normal. As, moreover, it is the normal forms of cells which are found, and as they do not show pathological changes, the conclusion may be drawn that the leucocytes are quite outside the essential change in the blood. The change is only in the erythrocyte system.

Further, as regards the terminology, the word leucostasis is still applicable, since we are dealing with a stasis which is chiefly determined by colourless elements. More problematic is the designation leucosis or erythroleucosis. The term leucosis was formed and used for diseases in the systems which produce leucocytes. For diseases in the erythrocyte-producing system other words are used : anemia, erythemia, etc.

In the leucosis of fowls there were now two ways to

go : either to give up the word leucosis as a designation for the intravascular and anemic cases which must then be named anemia or erythrosis, or, as hitherto, to use the word leucosis for all 3 forms, their etiology being the same. As it appears from the above I have provisionally chosen the latter way.

Finally, without making any attempt to enter upon an actual analogization, I shall make mention of some parallel cases from human pathology. In pernicious anemia of man large lymphoid cells occur in the bone-marrow, which are sometimes regarded as myeloblasts (Nægeli), sometimes as mother-cells of myelocytes as well as of erythroblasts (Pappenheim, Klein), sometimes as erythrogonies (Helly). My own experiments have led me to accept Helly's view, that we have before us lymphoid pre-phases of erythroblasts (erythrogonies). These cells, with reference to structure and staining, completely resemble the erythrogonies of the fowls.

Further, it has now proved (Ellermann) that in certain cases of pernicious anemia, one finds these cells, not only in the bone-marrow, but also intravascularly in the liver and spleen. Thus we have here a condition which on a smaller scale repeats the leucostasis in fowls. Also in pernicious anemia, erythrogonies may be found in the blood. Earlier findings by Meyer & Heineke seem explicable in this direction ; and previously Ferrata has described a case of pernicious anemia, in which numerous lymphoid promegaloblasts (erythrogonies) were found in the blood preparations.

Some cases which remind one very much of the intravascular lymphoid leucosis of fowls, are recorded by Pappenheim under the designation : erythroleucemia. One of the cases was originally erroneously explained as leucemia by Pappenheim, but renewed researches showed that the leucemia cells in the blood were not leucocytes, but, on the contrary, low pre-phases to erythrocytes. Ferrata & Negreiros-Rinaldi record similar cases, and Lindbom too (Casus XII.).

These examples will be sufficient to show that also in the human pathology one may meet with lymphoidocytes which must be interpreted as erythrogonies, and that the cases in question, as regards the blood formation, bear a certain resemblance to the erythroleucosis of fowls. Especially it may be emphasized that the blood formation in the disease in the fowls is the same in principle as in the pernicious anemia of man, as numerous unripe forms, viz. erythrogonies and megaloblasts, are formed by the regeneration. The process is much more pronounced in the disease in the fowls than in man, but the difference is chiefly quantitative.

IX

FINAL CHAPTER

THE leucosis of fowls is, as mentioned, for the present the only leucosis which can be transferred to healthy animals, and which thus makes possible experimental work and comparative-pathologic reflections. Besides, fowls have several advantages as experimental animals. For one thing they are of a suitable size, which in spite of the rather low percentage of takes makes it possible to carry out the experiments. In the next place, the work is facilitated by the fact that the specific cell granules are large and stain easily, while the bone-marrow is of a structure which is simple and perspicuous, so that the interpretation of the histological pictures, even in pathological conditions, does not offer invincible difficulties.

The great importance of experimental work needs no further pointing out. Thus we saw as regards the leucosis of fowls, that the experiments at once gave a result, making clear the infectious nature of the disease. Of course, in the beginning, the work could not be otherwise than uncertain and groping. The normal histology of fowls was at that time very little cultivated, a difficulty which was, however, comparatively small compared with those met with in the study of the pathological conditions. It was not possible directly to co-ordinate the findings with the pictures known from human pathology, and there was such a great step from the normal to the pathological that it was impossible to trace the development. The difficulties were not decreased by that con-

fusion in concepts and terminology that characterized and partly still characterizes the doctrine of the blood diseases of man.

In the beginning it seemed natural to regard the leucosis of fowls as a well-defined disease with a fairly typical picture, and I was inclined to understand the differences between the cases more as stages in the development of the same pathological process than as deep-going differences. At this time it seemed natural to suppose, either that the disease was analogous with one of the types of the human disease, or that it was a special type, which could not directly be co-ordinated with any form of the leucosis in man. Further study made it impossible to maintain the idea of a homogeneous process. On the contrary, such great differences appeared that it became necessary to set up the types described in the preceding chapters : the lymphatic, the myeloic and the intravascular lymphoid leucosis.

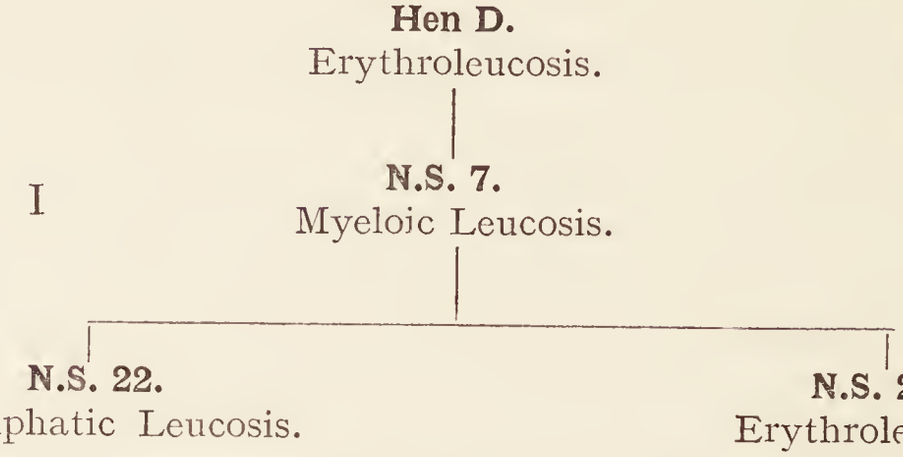
At the beginning of my studies it was my intention to work as far as possible independently of the doctrine of leucemia in man, so as not to be tied down to a form, which was perhaps only applicable by compulsion, and in order to be able to approach observations and problems without any prejudice. This working plan was temporarily to some degree favoured by the special nature of the cases in the first experimental strain. Gradually, as the experiments with the new strains progressed, there appeared, however, several features corresponding to conditions in the leucosis of man, and demanding designations. Here it would have been unnatural, and only liable to cause confusion if too many new terms had been introduced. In some cases this has been necessary, but as a rule I have kept to the terms in general use, and at the same time I have more and more adopted the designations and concepts known from the pathology of man. This may be regarded as a mistake or not, but at any rate it has been inevitable. The drawing of parallels, which theoretically ought to have been delayed till the final chapter, has in this

way slipped in throughout the description, and as the principle was thus broken, I have not scrupled to make direct comparisons between many of the phenomena described and similar ones taken from the pathology of man.

One of the essential objects of the work in hand has been to bring clearness in the histogenetic questions, since a knowledge of the histogenesis and nature of the pathologic forms of cells would be decisive for the understanding of the forms of the disease and of the individual pathologic processes. Without such knowledge further work would to a too high degree lack a firm foundation. The information derived from the researches relates mainly to the cells hitherto not sufficiently known—(1) transition cells and (2) large lymphocytes. "Transition cells" in myeloic leucemia have proved to be myeloblasts and their various stages of development (metamyeloblasts and poikilonuclears). In certain cases corresponding to the description already given of myeloic leucemia, besides these cells a great number of myelocytes are found in the blood. In another group of cases myelocytes are lacking and cells of the myeloblast series predominate. Further, the "large lymphocytes," or to put it more exactly, lymphoid cells (lymphoidocytes), which are often found in myeloic leucemia, but which are especially characteristic of the intravascular leucosis, have proved to be no real leucocytes in the accepted sense of the word, but erythrogonies (hemoglobin-free pre-phases of the erythroblasts). After this the intravascular lymphoid leucosis must be regarded in quite a new light. It is an erythroleucosis, or in ordinary words a severe anemia with pathological regeneration.

In preceding works I have emphasized the peculiar phenomenon, that the different forms of the disease may occur within one and the same experimental strain. Such a change of type appeared in strains D, E and H. Very illustrative are the conditions of strain D, which only comprises two experimental generations,

but which, in spite of this, presents all three types of the disease.



While a change from myeloic to lymphatic type or the reverse only occurred a few times, cases of erythroleucosis within all the strains were a common occurrence, no matter what character they had. *The different pictures are thus produced by one and the same virus.* Though it may appear peculiar that myelosis and lymphadenosis have the same etiology, it is, however, seen from a general pathologic point of view, just as remarkable that the same virus is able to produce as well leucemic hyperplasias as a severe anemia of the pernicious type, *i.e.* primarily a destructive process. Though it is well known that types of disease are abstractions, and that the individual case is the resultant of a complex of endogenous and exogenous factors, still the various forms in which the leucosis of fowls manifests itself are surprising and for the present perhaps without parallel.

Possibly these experiences may be of importance to the pathology of man. I have previously (1911) made an attempt to throw light upon the pernicious anemia of man, of which the etiology is unknown, from the anemic cases of the leucosis of fowls. Even Meyer & Heineke had called attention to the histologic resemblance between pernicious anemia and myeloic leucemia, particularly to the fact that in both these diseases there was a myeloic transformation in various organs. In this connection I emphasized various points of resemblance in the clinical course, but the chief argument was the reference to the

fact that the virus of the leucosis of fowls produced anemic as well as leucemic cases. After this it was at any rate possible that the pernicious anemia of man might be an infectious disease which was closely akin to, possibly etiologically identical with, leucemia. The idea has been discussed, but has so far found no acceptance. Only Ferrata and his collaborators have from other points of view pronounced in favour of the relationship (but only histogenic) between leucemia and pernicious anemia. The question is to some extent outside the scope of this treatise, and so I shall only mention a few points. When Domarus emphasizes that the leucopenia in the pernicious anemia is in striking contrast to the augmented leucoblastic of leucemia, this is certainly as a rule correct, but leucopenia is by no means unknown in leucemia since the symptom may be found in acute leucemia. Further, it must be mentioned that the argument provided by comparative pathology has become much more weighty than it originally was, since the three different forms of the leucosis of fowls have been set up, and since it has been shown that anemias are not rare exceptions, but that the whole group of "intravascular lymphoid leucosis" must be understood as severe anemias with strong atypical regeneration (pernicious type). Also the peculiar course, which is frequently met with, that after a period of severe anemia a remission with normal blood findings occurs, cannot but bring to mind the remissions in the pernicious anemia of man.

Some time ago I emphasized that there were some transition forms between myeloic leucemia and pernicious anemia, viz., partly leucemias with particularly strongly pronounced anemia, partly the so-called leucanemias. Transition cases will always with difficulty be recognized as such in clinical nosography which must necessarily keep to typical pictures as long as the etiology is unknown. We are much better off in the case of the experimental disease of fowls, in which we know that the cases are produced by the specific virus, and in which it is not necessary to reject the "atypical" cases. Whereas the

lymphatical leucosis, according to my experience, until now generally presents a pure type,[1] transition forms between myeloic leucosis and erythroleucosis very often occur. Here we approach a point important for the understanding of the relation between leucemia and anemia, viz., how we are to understand the myeloic hyperplasia in the individual case. As the principle of classification of the forms of the leucosis of fowl is quite morphologic, so that the three types correspond to the three systems of tissue—the lymphatic, the myeloic and the erythroic—it is natural to speak of mixed cases, when, *e.g.*, in a case of erythroleucosis considerable myelocyte infiltrations appear in the liver, or when in conjunction with myeloblast leucemia and infiltrates of myeloblasts in the organs a well-pronounced leucostasis occurs with partial atrophy of the trabeculæ of the bone-marrow. I am not disinclined to think that in such cases we are dealing with co-ordinated processes ; the possibility that one process might be primary and the other secondary may, however, be mentioned ; not because there are firm holds for this, but because such a consideration has found a certain acceptance in human pathology. Here the hyperplasia of the myeloic leucosis is looked upon as a primary process, whereas the myeloic hyperplasia in pernicious anemia, which may often be rather considerable, is regarded as secondary and of " compensatory " nature. Considering the leucosis of fowls the question of the genesis of the myeloic hyperplasia ought perhaps to be recon-

[1] The existence of a mixed leucemia, *i.e.* a mixture of myelosis and lymphadenosis as regards man, has been proved by several authors (Herz, Türk, Franck & Isaac), but the cases are, at any rate, very rare. In the strain H, I have had a case of leucosis of fowls (N.S. 271) which may perhaps be regarded as such a mixture. There was—(1) An indubitable aleucemic myelosis : infiltrates in the liver and spleen. (2) The follicles of the spleen were well developed and frequently contained germinal centres which were twice as big as normal. In the liver periportal accumulations of small lymphocytes. (3) A well-pronounced leucostasis (erythrogonies) in the capillaries in liver and bone-marrow. (Blood preparations during life showed erythrogonies and erythroblasts.)

sidered and, as far as possible, experimentally investigated too.

Apart from such cases as must be understood as combinations of myeloic and anemic leucosis, most of the cases were on the whole pure. The morbid process begins in one single system, and usually keeps to this during the whole course of the disease. A lymphatic case remains lymphatic, a myeloic or an anemic case in the same way keeps its character from the beginning of the disease to the death of the animal. A change in the type of disease is not seen in the individual animal.

Now the question arises, what it is that conditions the appearance of the different forms of the leucosis of fowls. Is it peculiarities of constitution that cause certain individuals to be predisposed to anemia, others on the contrary to myeloic or lymphatic hyperplasia, or have different external factors played a part ? The individual predisposition is a factor which must undoubtedly be taken into consideration. Thus it is known (Schauman) that the bothriocephalus anemia is rare, though the tapeworm is common in the intestine of man in certain regions. We have thus the strange phenomenon that the specific cause, viz. the poison of the worm, is ineffective in most human beings. Only in a few in a thousand of the infected do we find the special predisposition which is a necessary condition of the genesis of the anemia. That peculiarities in these individuals and not in the worm are the decisive factors is clearly shown by the family occurrence of the cases which Schauman has pointed out. In accordance with this Schauman has strongly emphasized the significance of the predisposition for the essential pernicious anemia, and in the case of this disease, too, we have a series of reports of family occurrence.

Whether a family predisposition is of importance or not as to the leucemia of fowls must for the present remain doubtful, as we have no investigations to guide us on this point ; but the analogies favour the belief. With regard

to the spontaneous cases we might perhaps imagine the possibility that the place of entrance and the ways by which virus is spread in the organism would determine the type of the disease. This conjecture was put forward by Pappenheim, and at first glance seems to provide a likely explanation. In the experimental disease, however, the way of infection is always the same (intravenous injection), and notwithstanding this the different types arise. Virus is thus carried with the blood to all the organs, and when the effect is different it must be because the predisposition of the tissue is different, so that one animal reacts with anemia, another with myeloic or lymphatic hyperplasia. Perhaps we must also reckon with a certain difference in the virus. The experimental strains, as it seems, show a tendency to preponderance of a particular type of disease. The possibility that one virus might mainly be myelotropic, another more lymphotropic, would scarcely be without parallel in pathology; but at any rate we are dealing with rather complex conditions, the unravelling of which will claim further research. The views advanced must not be taken for more than they are—an attempt at a provisional orientation.

The question of the nature of the leucosis of fowls has to a great extent found its reply in the preceding chapters, in which the analogies inevitably obtrude themselves, and the very possibility of so wide a parallelization is eloquent in itself. Regarding the disease as an entirety, even the greatest sceptic will hardly be able to deny that the leucosis of fowls, viewed more broadly as well as in detail, strikingly recalls the leucosis of man. Apart from the anemic cases, which are mentioned above, and keeping to the myeloic and the lymphatic cases, hyperplasias in the individual systems of blood-forming tissue are found which regularly involve the death of the animal, and in which microbes cannot be detected by direct examination or cultivation. The myeloic cases which may be either leucemic or aleucemic, show typical myelocytes as well as less differentiated cells (myeloblasts). As well myeloic as

lymphatic cases may at times be combined with tumour building (leucosarcomatosis), etc.

This by no means implies that there are no differences. It would be absurd to expect that the features of the disease in two such remote kinds should be identical in every particular. Thus the lymphatic glands are lacking in fowls, which involves that the lymphatic leucosis of fowls is in some ways different from that of man, though the essential feature, the hyperplasia of the lymphatic system, is the same. This, however, is a more external difference. More important are the following facts. (1) According to past experience the lymphatic leucosis of fowls is always aleucemic. (2) The hyperplasia is always large-celled. The new formed cells are large pathologic lymphoblasts which often have a striking tendency to form stroma.

In myeloic leucosis there is only exceptionally and temporarily formed an excess of ripe polynuclears ; but, as a rule, it is the myelocytes and especially cells of the myeloblast series which characterize the picture. In erythroleucosis the forming of erythrogonies often takes place on a scale which is far beyond the corresponding phenomenon in the pernicious anemia of man.

This development of pathologic, rather undifferentiated forms of cells is thus in all three forms of the leucosis of fowls more pronounced than in the corresponding diseases of man.

The smaller differentiation of the hyperplastic cells in the leucosis of fowls is perhaps due to the lower phylogenetic position of the fowls ; but it is noteworthy that the three kinds of cells—myeloblasts, lymphoblasts and erythrogonies—in spite of their all three appearing as lymphoid cells, constantly remain morphologically and functionally different. Though the types of disease may sometimes be mixed, there are no transition forms between them, regarded cytogenetically. The theory, previously advanced by me, that the intravascular lymphoid leucosis was perhaps a primordial cell leucosis must, of course, after our latest experience, be given up, and on the whole there will be no room for such a theory in the leucosis of fowls. This disease,

therefore, affords no support for the unitarian school in hematology ; on the contrary, experience goes to show that the concept of primordial cells in man (*e.g.* Pappenheim's lymphoidocytes which may develop into erythroblasts or into myeloblasts) is based on erroneous interpretations. This I have had confirmed by my own examinations of cases of leucemia in man.

The pathology of leucosis, of course, involves many problems of which, however, only a few have as yet assumed a definite form. Some of the questions have been touched on in the preceding pages, so I shall confine myself to dealing in more detail with only a single one, viz., the genesis of leucemia ; not because the researches have given any result in this respect, but because it is a point on which one would be inclined perhaps to entertain expectations beforehand. The fact is that in man the myeloic leucosis is virtually always leucemic, while the lymphatic leucosis is now leucemic, now aleucemic. Various investigators have tried to explain the case, but none of the theories were proof against criticism, and in reality at present we are out of our depths. Neumann's theory, that leucemia was dependent on the bone-marrow being attacked, has now only historical interest. The same may be said of Banti's theory : that the new-built tissues, by simply growing into the vessels, caused the leucemia. Ribbert assumed that the aleucemic cases arose by an emigration from the vessels of the new-built cells. We have no histological base for this, and at any rate we should want to know why the emigration took place in those cases, and not in others (the leucemic cases). In a previous work with Oluf Bang, I have advanced the theory that in the aleucemic cases there could be an agglutinine effect, which kept the new-formed cells in the depots. Such substances have not, however, as yet been detected. But whether it be agglutinines, a chemotactical effect, or ordinary differences of reaction, the possibility of a chemical effect ought certainly to be taken into consideration. Finally, there might perhaps be differences in the power of emigration of the new-formed cells.

Unfortunately the leucosis of fowls is not well suited for experiments on the genesis of leucemia because the myeloic form is nearly always leucemic, whereas the lymphatic form always is aleucemic. In a previous work I have advanced the proposition that the leucostasis was a necessary supposition for the leucemia. Our experience with the experimental strain H, however, shows that a pronounced myeloic leucemia may be found without leucostasis, and that this is a phenomenon which does not concern the leucemia. The increase of leucocytes in the streaming blood, on the other hand, is a factor to which must still be attached some importance. This increase may in certain cases be very considerable—so considerable that the blood may be regarded as a self-growing tissue. In several cases the mitoses are, however, fairly scarce, so that an increase of the leucocytes of the blood can hardly be decisive for the leucemia. The leucosis of fowls thus gives us no contribution to the understanding of the genesis of the leucemical blood-change in man.

If now we ask what conclusions may be drawn from the leucosis of fowls to the analogic disease of man as regards etiology, it must at once be emphasized that we can of course only speak of analogic inferences, *i.e.* working hypotheses founded on comparison, but without independent worth until they have been verified. In a preceding part I have tried to prove that the theory of infection stands on a firmer ground than the other etiological theories. To me it seems undeniable that the discovery of the infectious character of the leucosis of fowls lends an essential support to the theory. Therefore I find it most natural for the present to reckon with a specific virus as the cause of the leucosis in man, but as said before, this is only a hypothesis. Likewise, in my opinion, one ought to take up for further consideration the possibility that leucemia and pernicious anemia might be etiologically identical diseases.

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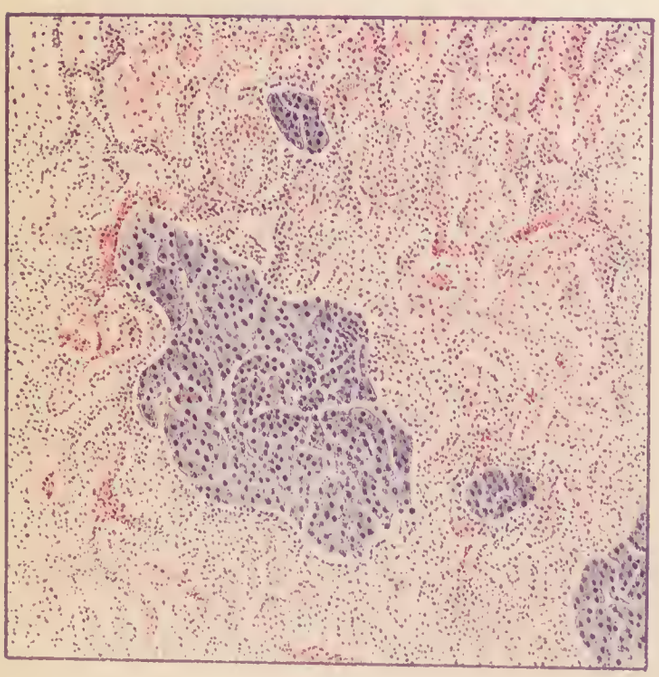

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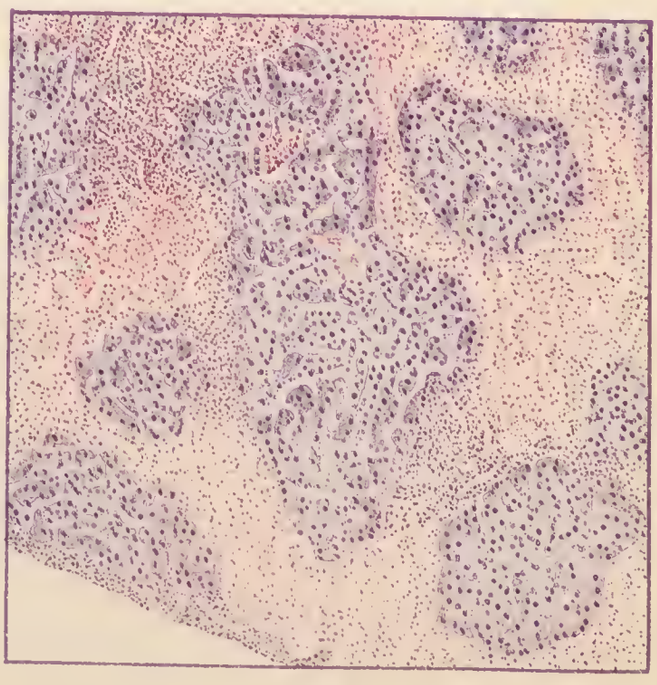

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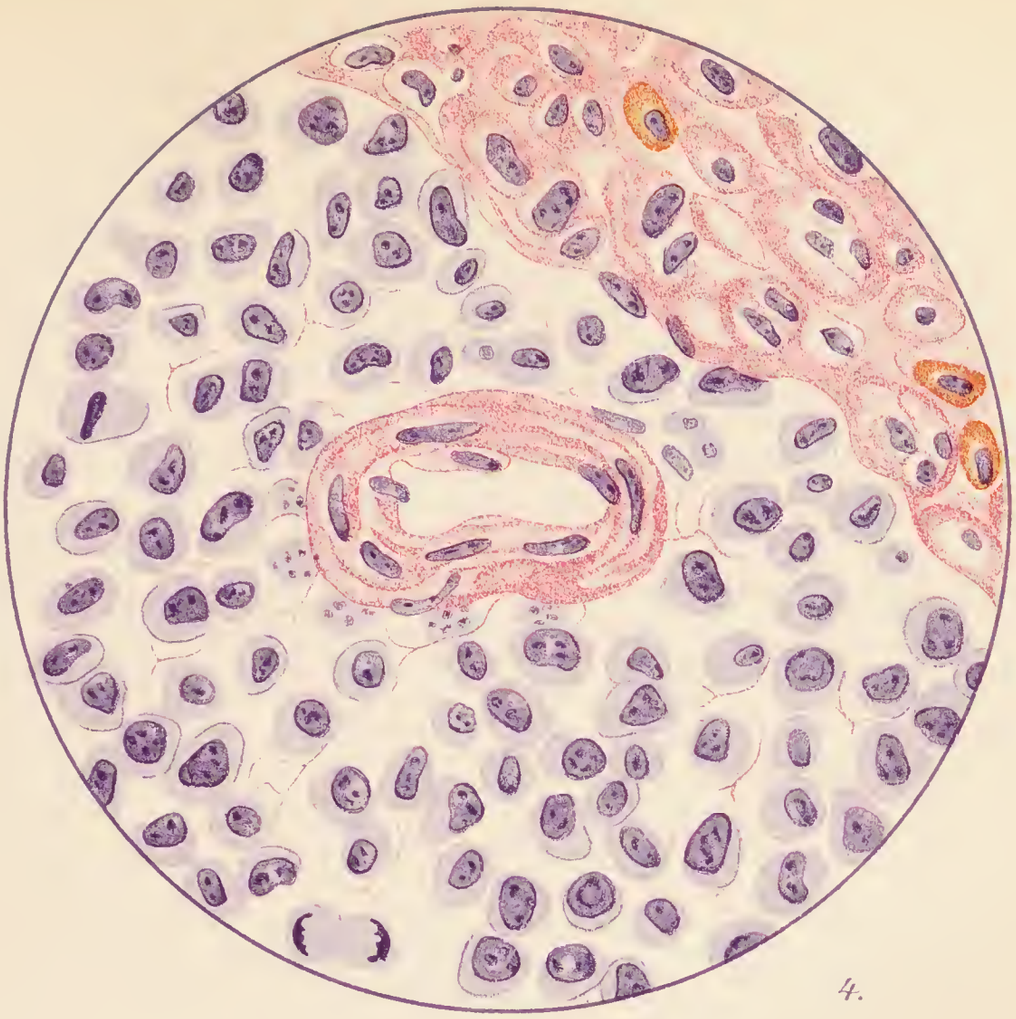

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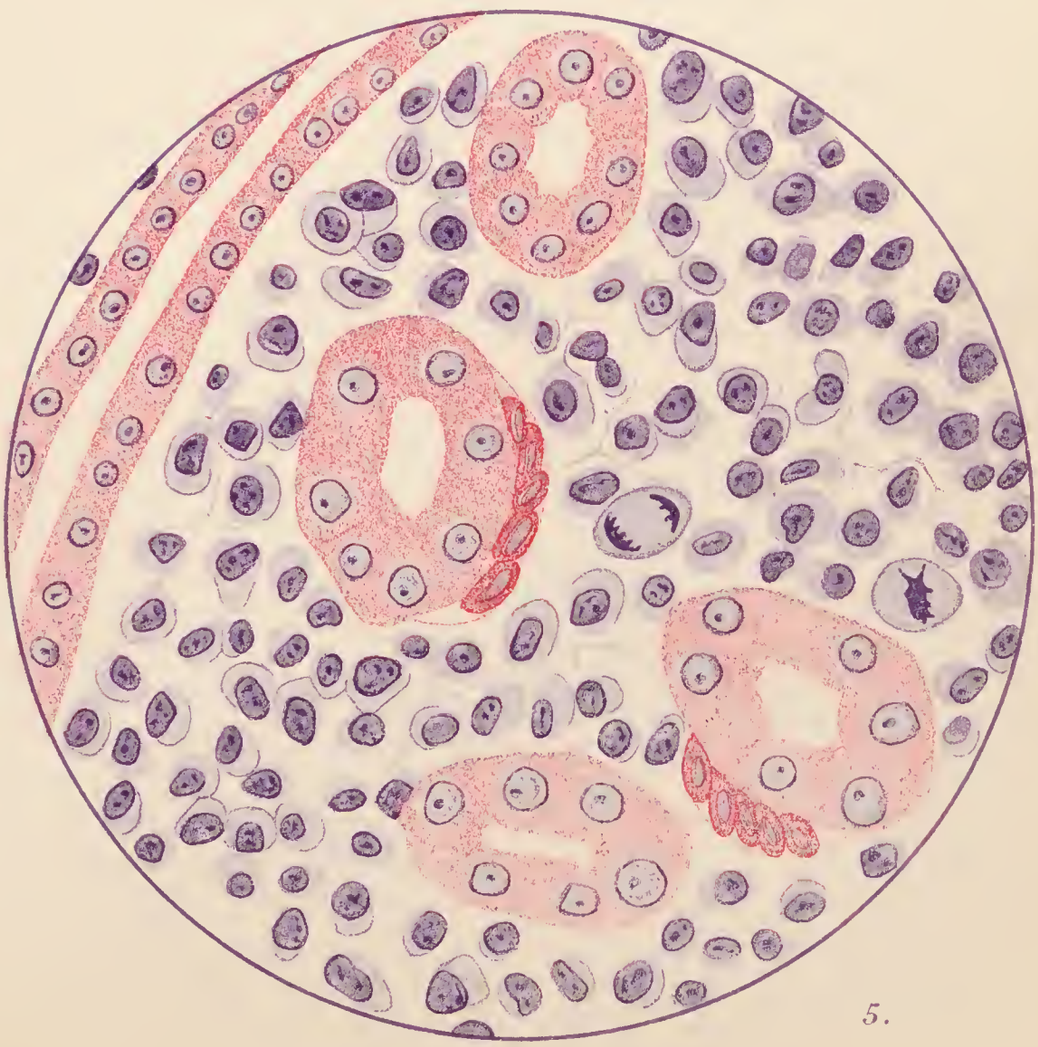

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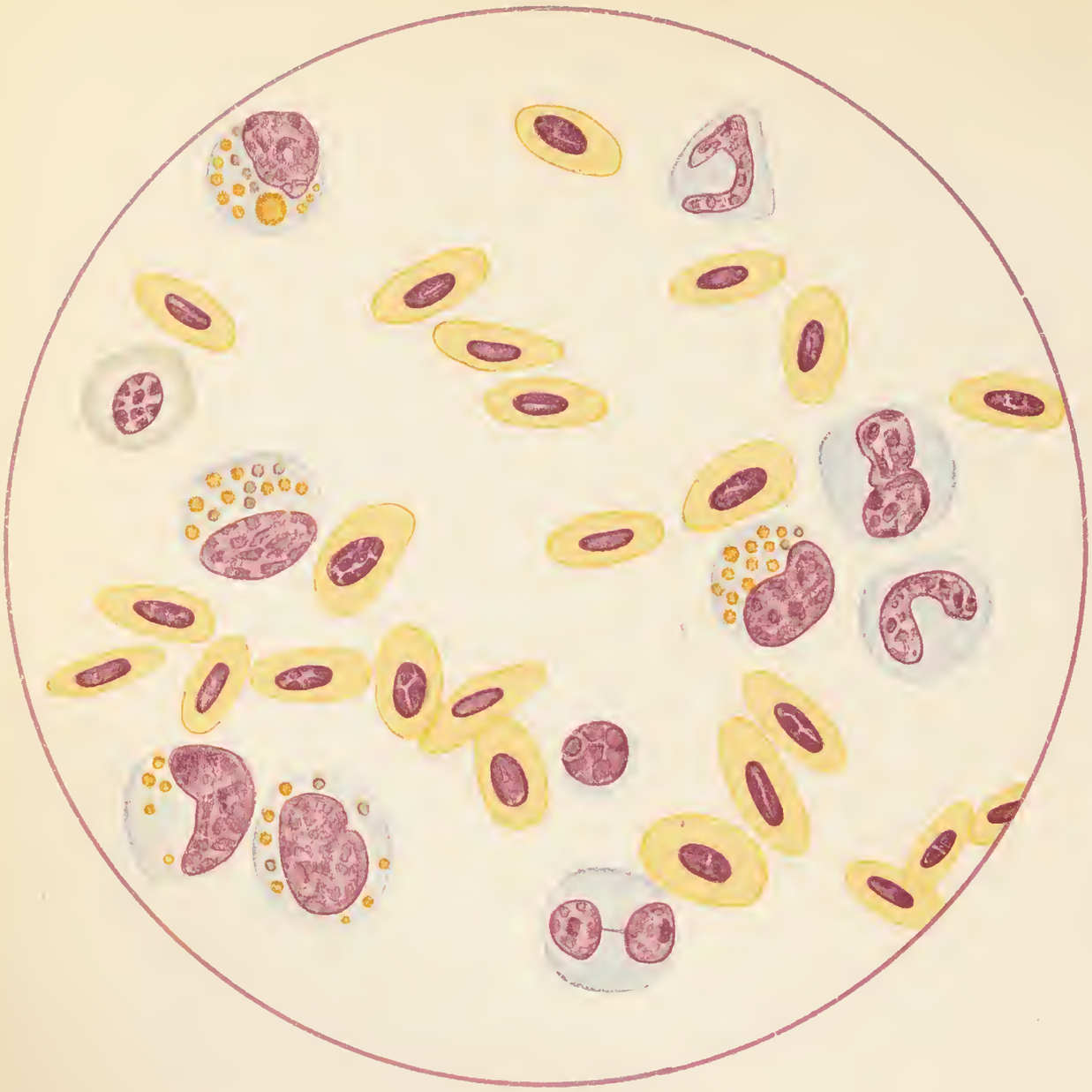

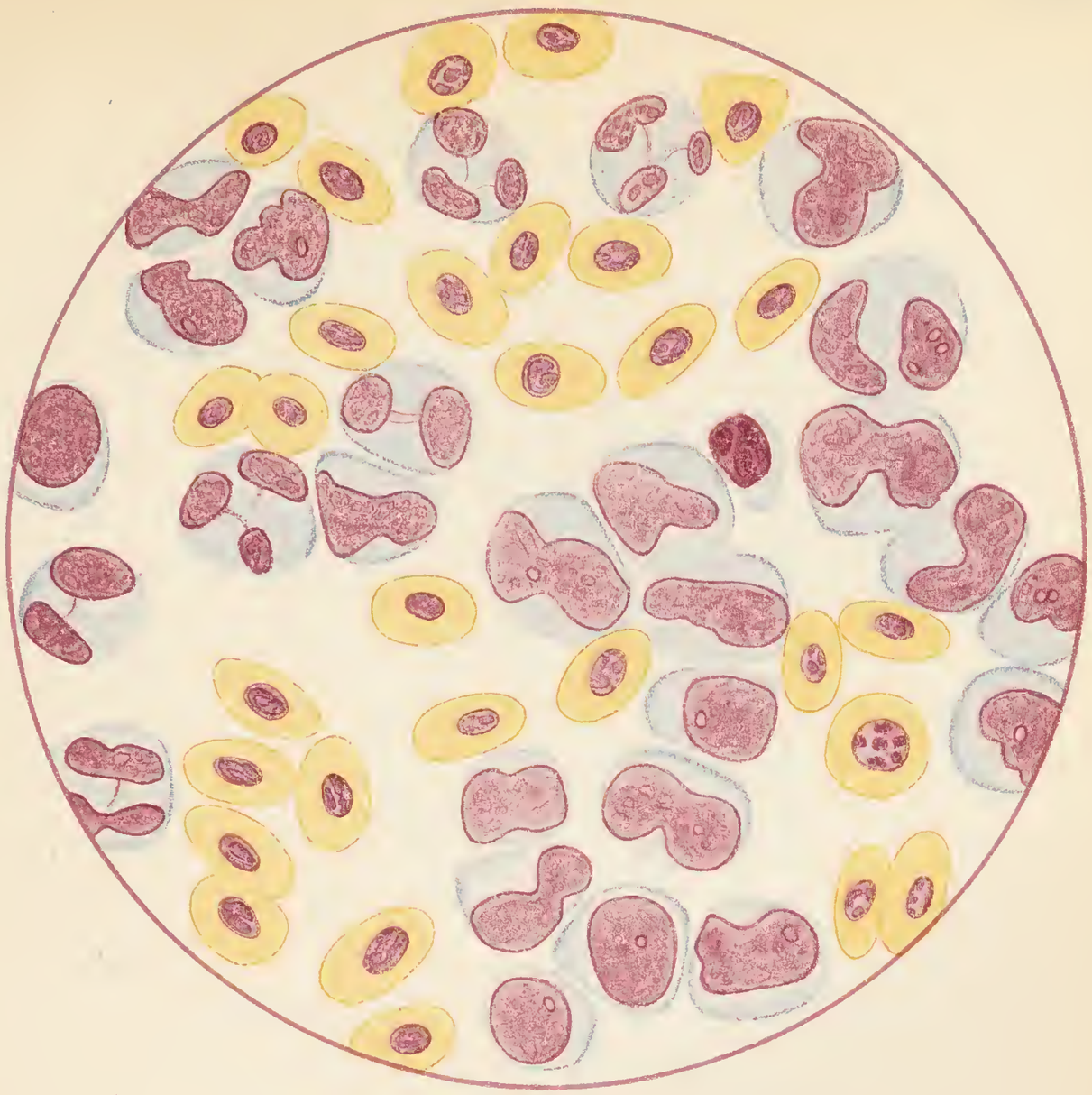

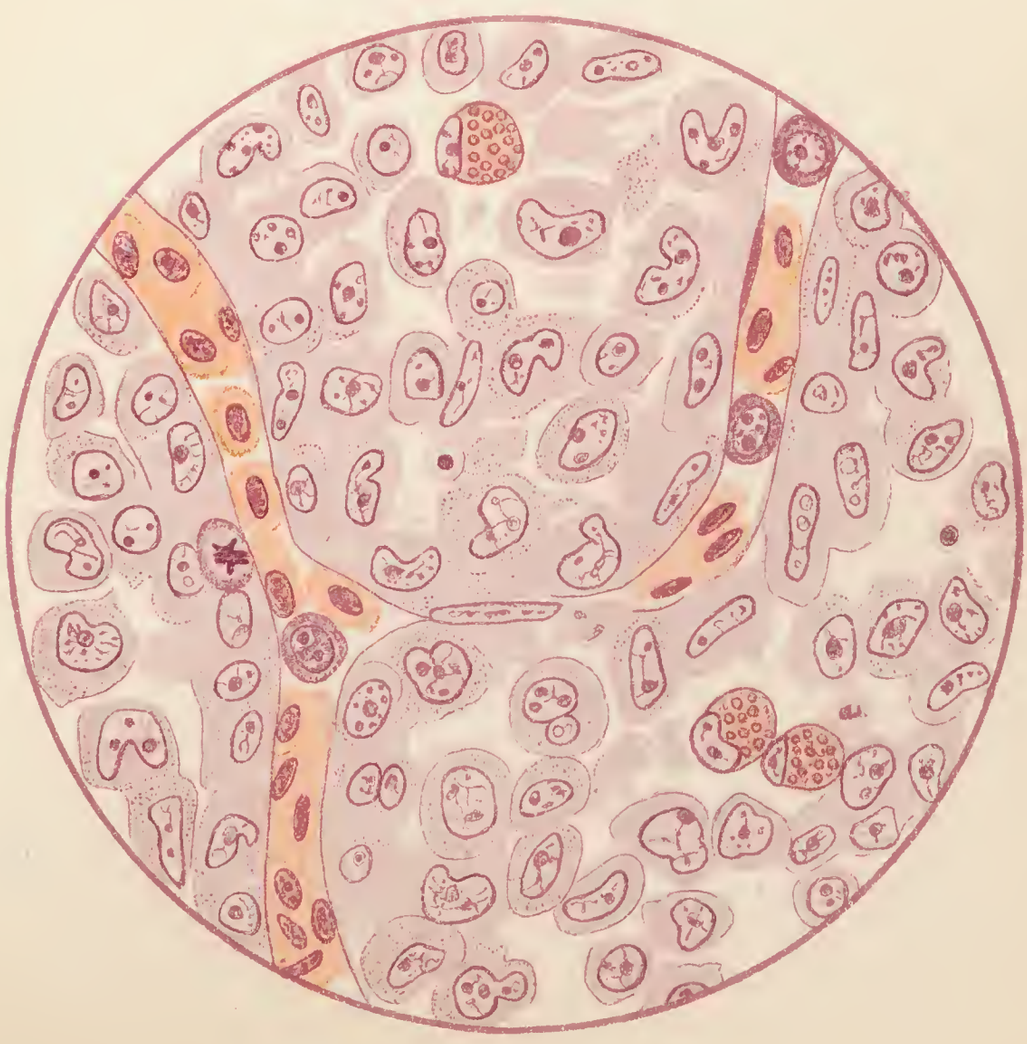

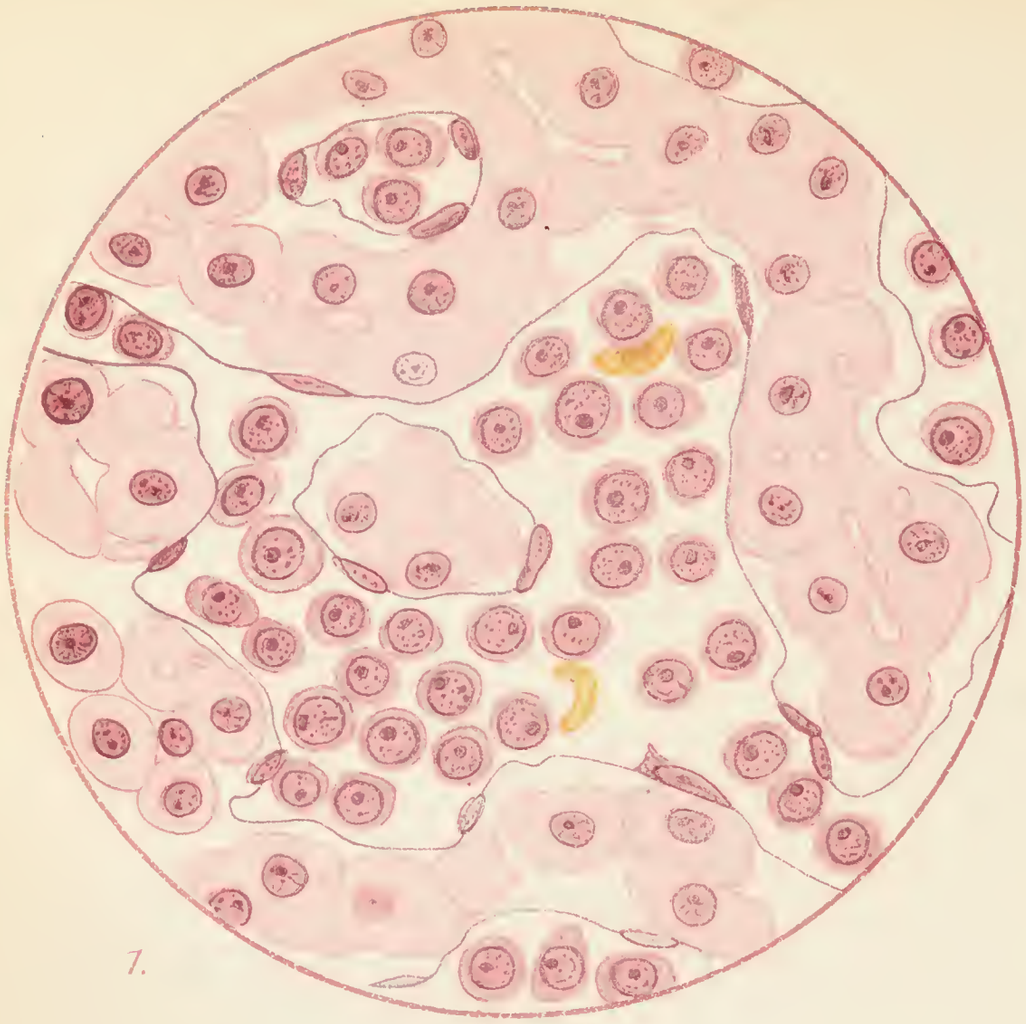

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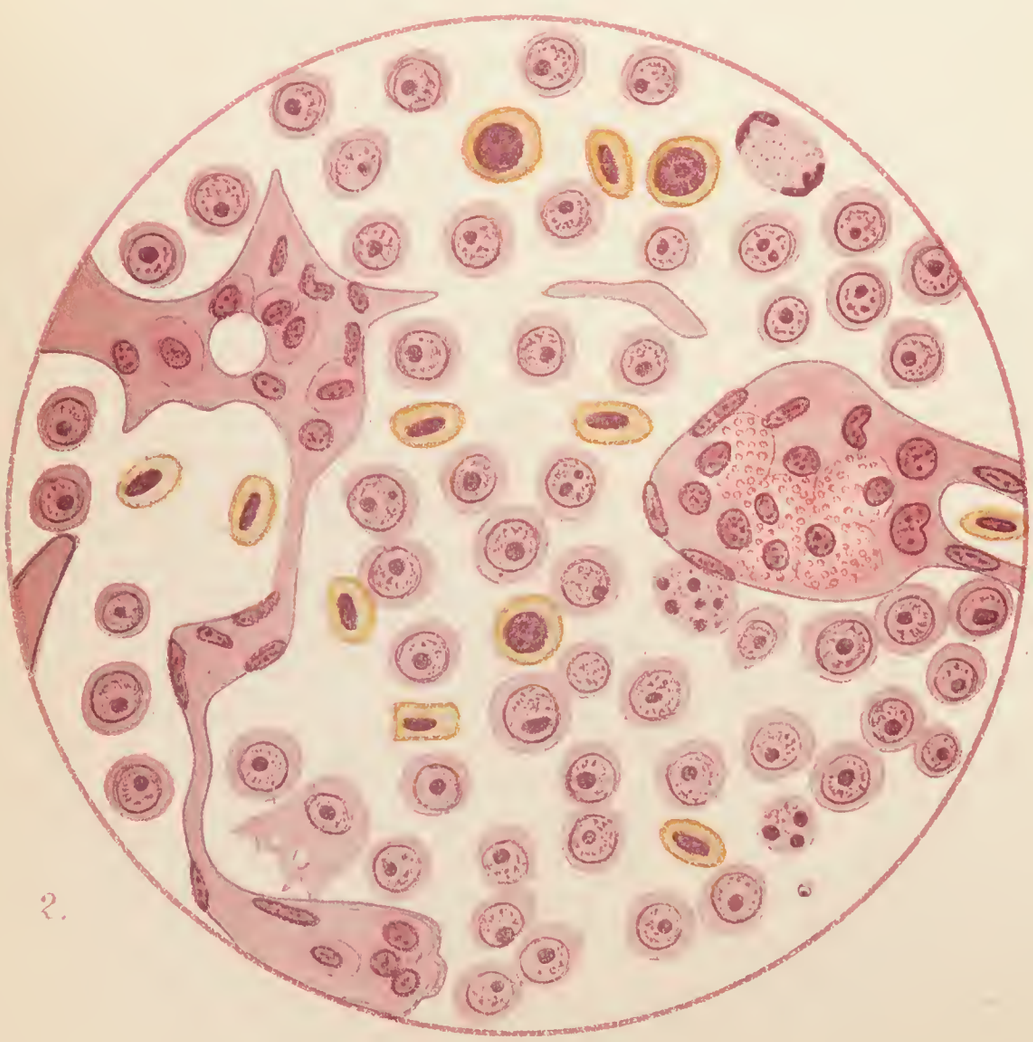

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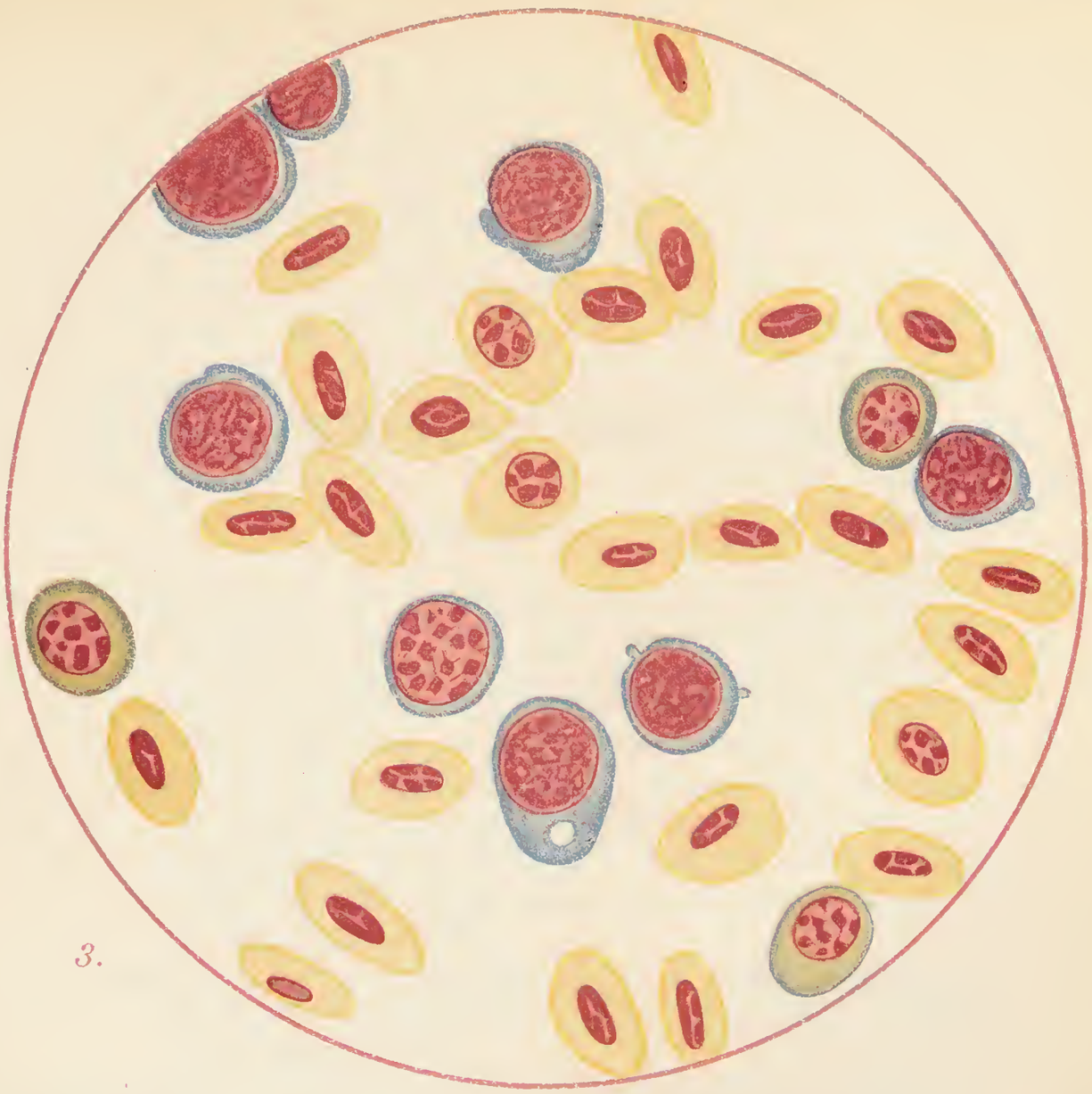

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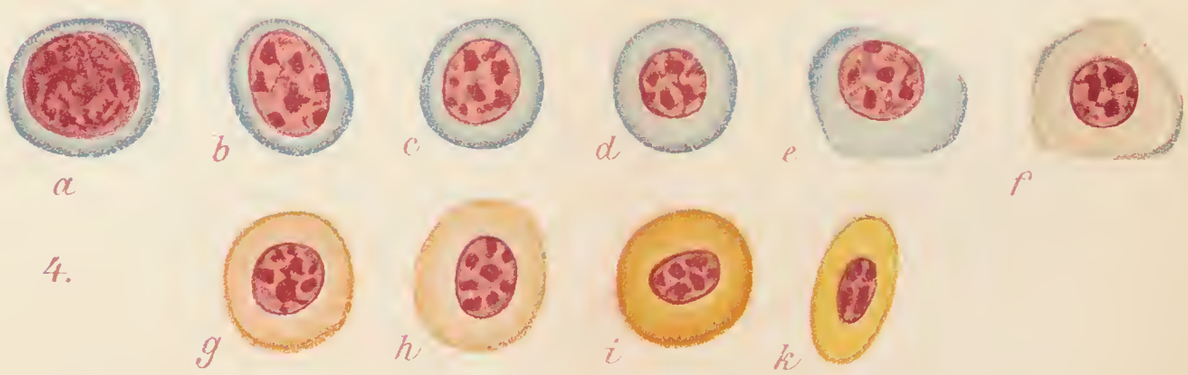

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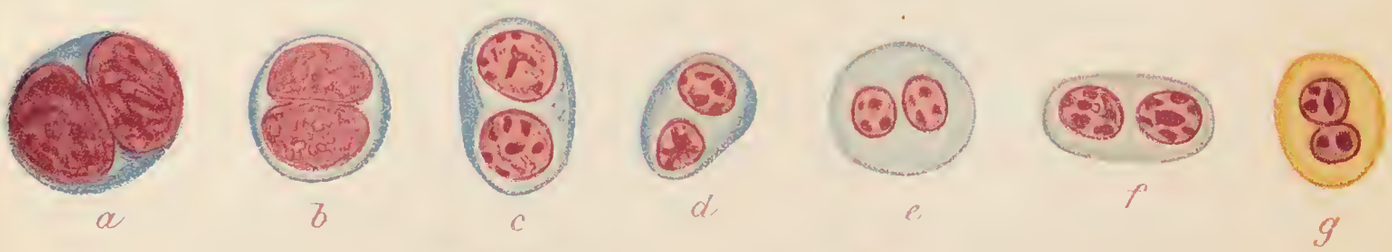

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EXPLANATION OF THE PLATES

PLATE I

FIG. 1.—*Section of liver in lymphatic leucosis.*—Synoptic picture. Staining in hematoxylin-eosin. Well-developed, medium-sized periportal lymphocyte infiltrations are seen. The liver tissue in between them is normal. No accumulation of cells in the capillaries.

FIG. 2.—*Section of normal spleen.*—Slight magnifying. Staining in hematoxylin-eosin. Pulp tissue predominant. In the middle of the follicles a germinal centre, which came out much more distinctly in the preparation than in this reproduction.

FIG. 3.—*Section of spleen in lymphatic leucosis.*—Slight magnifying. Staining in hematoxylin-eosin. The follicles large and closely placed.

FIG. 4.—*Section of spleen in lymphatic leucosis.*—High magnifying. Colouring in hematoxylin-eosin. The pulp tissue is seen to the right, to the left the edge of a follicle with its artery. The follicle contains large cells, lymphoblasts. Two mitoses are seen.

FIG. 5.—*Section of kidney in lymphatic leucosis.*—High magnifying. Between the renal tubules is seen a considerable infiltration with lymphoblasts. Two mitoses are seen.

PLATE II

FIG. 1.—*Blood from myeloic leucemia (myelocyte type).*—Five myelocytes, 1 myeloblast, 2 metamyeloblasts, 1 polynuclear, 1 lymphocyte, 1 erythroblast.

FIG. 2.—*Blood from myeloic leucemia (myeloblast type).*—Myeloblasts, metamyeloblasts, poikilonuclears, 1 lymphocyte.

FIG. 3.—*Myeloblast mitoses in blood preparation.*

FIG. 4.—*From a blood preparation in myeloblast leucemia.*—Three myeloblasts, 1 lymphoidocyte.

FIG. 5.—*Bone-marrow in myeloblast leucemia.*—Preparation of section : Sublimate-Hematoxylin-eosin.

In the hyperplastic trabeculæ chiefly myeloblasts, few myelocytes. Sinus very narrow.

PLATE III

FIG. 1.—*Section of the liver.*—Staining in hematoxylin-eosin. The capillaries are very much dilated and filled with lymphoidocytes, among which single erythrocytes are to be seen.

FIG. 2.—*Section of bone-marrow.*—The same staining. To the left in the field of view, very atrophic trabeculæ, to the right a trabecula with scarce myelocytes. The fat tissue has disappeared. The sinuses are enormously dilated and full of lymphoidocytes. Few erythrocytes and erythroblasts. Above to the right, a lymphoidocyte in mitosis.

FIG. 3.—*Blood picture in intravascular lymphoid leucosis (leucemical form).*—Besides normal erythrocytes, erythroblasts with a round, distinctly structured nucleus are seen. Further erythroblasts with grey or bluish protoplasm, and lymphoidocytes. The latter have usually a homogeneous nucleus, in a single one, however, separated chromatin particles are seen.

FIG. 4.—*Transitions from lymphoidocyte to erythrocyte.*—(*a*) Lymphoidocyte. (*b*, *c*) Transition forms with structured nucleus. (*d*, *e*) Polychrome erythroblasts. (*f*, *g*, *h*) Hemoglobin-poor erythroblasts. (*i*) Erythroblasts with greater hemoglobin content. (*k*) Ripe erythrocyte.

FIG. 5.—*The same series of development in cells with twin-nuclei.*—(*a*, *b*) Lymphoidocyte. (*c*, *d*) Transition forms. (*e*, *f*) Polychrome erythroblasts. (*g*) Erythroblast with greater hemoglobin content.

FIG. 6.—(*a*, *b*) *Lymphoidocytes in mitosis.*

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